

Description

2-ACYLAMINOTHIAZOLE DERIVATIVE OR SALT THEREOF

5 Technical Field

The present invention relates to novel 2-acylaminothiazole derivatives or salts thereof which are useful as medicaments, especially a thrombocytopenia treating agent, and medicaments comprising one or more said
10 compounds as active ingredients.

Background Art

Platelets are non-nucleated blood cells which play a main role in physiological hemostasis and pathologic
15 thrombus generation. Platelets are constantly produced in vivo from megakaryocytes, precursor cells. Platelets are, like other blood cells, produced from multipotential stem cells. Multipotential stem cells become megakaryocytic precursor cells, from which megakaryoblasts,
20 promegakaryoblasts and megakaryocytes are formed in this order. During maturation of the megakaryocytes, immature megakaryocytes conduct DNA synthesis only without cell division to form polyploids. Thereafter, maturation of cytoplasm begins to form platelet separation membranes, and
25 the cytoplasm is split to release platelets.

Meanwhile, a decrease in platelets due to various hematopoietic disorders in chemotherapy, radiotherapy or the like of anemia, myelodysplastic syndrome or malignant tumor induces serious conditions such as invitation of bleeding tendency. Therefore, various attempts of technical development for increasing platelets have been made for the purpose of treating the same. At present, a potent method for treating thrombocytopenia is platelet transfusion. However, a sufficient amount of platelets is not yet supplied, and life of platelets transfused is short. For these reasons, it is hard to satisfactorily improve thrombocytopenia. Moreover, platelet transfusion involves problems such as viral infection, production of alloantibody and graft versus host disease (GVHD). Accordingly, the development of medications for relaxing an inhibitory state of a hematopoietic function induced by various diseases or therapies and accelerating recovery of the number of platelets has been expected.

Under these circumstances, it has been reported that thrombopoietin (hereinafter referred to as TPO) which is a main factor participating in division to megakaryocytic cells and is a c-Mpl ligand is cloned to stimulate division and growth of megakaryocytic cells and accelerate production of platelets (Kaushansky K. et al., Nature, 369, 568-571, 1994; Non-patent Document 1). TPO has already been subjected to a clinical test as a platelet increasing agent,

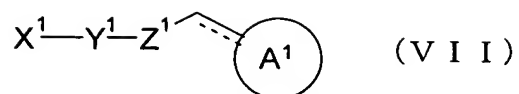
and usefulness and tolerance in humans are being confirmed. However, in a clinical test of PEG-rHuMGDF (TPO whose 163rd amino acid seen from the N-terminal has been modified with polyethylene glycol) which is a type of TPO, a neutralizing
5 antibody has been confirmed (Li J. et. al., Blood, 98, 3241-3248, 2001: Non-patent Document 2, and Bassar R. L. et al., Blood, 99, 2599-2602, 2002: Non-patent Document 3).

Accordingly, there is a fear of TPO immunogenicity.

Further, since TPO is a protein, it is decomposed in
10 digestive organs, and is thus not practical as an oral administration drug. For the same reason, a low-molecular peptide is not considered either to be practical as an oral administration drug. Under these circumstances, the development of an orally administrable non-peptide c-Mpl
15 ligand with less immunogenicity has been under way for treatment of thrombocytopenia.

As the foregoing compounds, benzodiazepine derivatives (Patent Document 1), acylhydrazone derivatives (Patent Document 2), diazonaphthalene derivatives (Patent Document
20 3), pyrrocarbazole derivatives (Patent Document 4), pyrrophenanthridine derivatives (Patent Document 5) and pyrrophthalimide derivatives (Patent Document 6) have been known.

WO 01/07423 (Patent Document 7) describes that
25 compounds represented by the following general formula (VII) have a platelet increasing function.



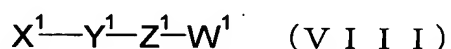
(As to symbols in the formula, refer to the document.)

The document describes the compounds containing

thiazole which may be substituted as X¹ and -NHCO- as Y¹. In the present invention, however, R³ in the compounds of the invention is not substituted with a substituent having an A¹ group such as a thiazolyl group in the document. Moreover, regarding compounds in which the 5-position of thiazole is substituted with a lower alkyl substituted with a nitrogen atom, there is not any concrete disclosure by Examples or the like in the document.

WO 01/53267 (Patent Document 8) describes that compounds represented by the following general formula

15 (VIII) have a platelet increasing function.



(As to symbols in the formula, refer to the document.)

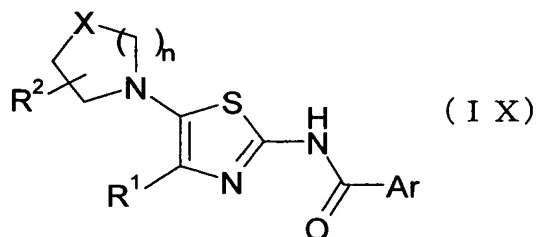
The document describes the compounds containing

20 thiazole which may be substituted as X¹ and -NHCO- as Y¹. In the present invention, however, R³ in the compounds of the present invention is not substituted with a substituent having a W¹ group in the document. Regarding compounds in which the 5-position of thiazole is substituted with a lower

alkyl substituted with a nitrogen atom, there is not any concrete disclosure by Examples or the like in the document.

WO 02/62775 (Patent Document 9) describes that compounds represented by the following general formula (IX)

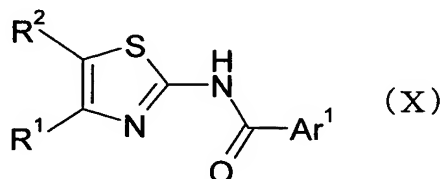
5 have a platelet increasing function.



(As to symbols in the formula, refer to the document.)

The document describes the compounds in which the 5-
10 position of 2-acylaminothiazole is directly substituted with a nitrogen atom. However, it does not describe compounds in which the 5-position of thiazole is substituted with a lower alkyl substituted with a nitrogen atom in the present invention.

15 WO 03/062233 (Patent Document 10) describes that compounds represented by the following general formula (X) have a platelet increasing function.



20 (As to symbols in the formula, refer to the document.)

The document describes the compounds in which the 5-position of 2-acylaminothiazole is directly substituted with a nitrogen atom. However, it does not describe compounds in which the 5-position of thiazole is substituted with a lower alkyl substituted with a nitrogen atom in the present invention.

In addition to the foregoing Patent Documents 7 to 10, 2-acylaminothiazole compounds are described as cholecystokinin and gastrin receptor antagonists in Patent No. 3199451 (Patent Document 11) or as compounds having antiinflammatory characteristics in Chemical and Pharmaceutical Bulletin, 25, 9, 2292-2299, 1977 (Non-patent Document 4). However, none of them indicate at all the platelet increasing function in the present invention.

Under such circumstances, the development of an orally administrable non-peptide c-Mpl ligand with less antigenicity has been in demand for treatment of thrombocytopenia.

	[Patent Document 1]	JP-A-11-152276
20	[Patent Document 2]	WO 99/11262 pamphlet
	[Patent Document 3]	WO 00/35446 pamphlet
	[Patent Document 4]	WO 98/09967 pamphlet
	[Patent Document 5]	JP-A-10-212289
	[Patent Document 6]	JP-A-2000-44562
25	[Patent Document 7]	WO 01/07423 pamphlet
	[Patent Document 8]	WO 01/53267

[Patent Document 9] WO 02/62775 pamphlet
[Patent Document 10] WO 03/062233 pamphlet
[Patent Document 11] Patent No. 3199451
[Non-patent Document 1] Nature, 1994, No. 369, p. 568-

5 571

[Non-patent Document 2] Blood, 2001, vol. 98, p. 3241-
3248

[Non-patent Document 3] Blood, 2002, vol. 99, p. 2599-
2602

10 [Non-patent Document 4] Chemical and Pharmaceutical
Bulletin, 1977, vol. 25, No. 9, p. 2292-2299

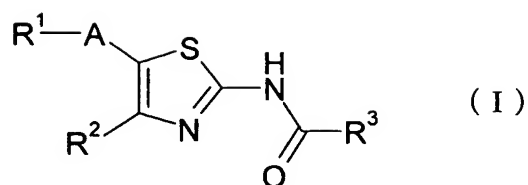
Disclosure of the Invention

The present inventors have assiduously conducted
15 investigations on compounds having a platelet increasing
function, and have found that novel 2-acylaminothiazole
derivatives have an excellent platelet increasing function.
They have thus completed the present invention.

That is, according to the present invention, the
20 following (1) to (15) are provided.

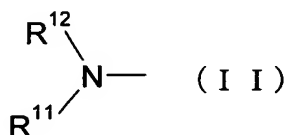
(1) A platelet increasing agent comprising a 2-
acylaminothiazole derivative represented by the formula (I)
or a pharmaceutically acceptable salt thereof as an active
ingredient.

25



[Symbols in the formula have the following meanings.

R^1 : a group represented by the formula (II), or cyclic



[Symbols in the formula have the following meanings.

R¹²: a lower alkyl, a cycloalkyl or a non-aromatic heterocycle, each of which may be substituted.]

R³: an aromatic heterocycle, an aryl or cyclic amino,
each of which may be substituted.]

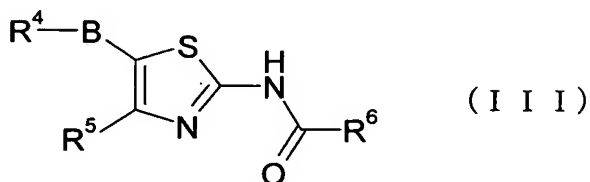
(2) The pharmaceutical composition of (1), wherein A is methylene.

(3) The pharmaceutical composition of (2), wherein R² is thienyl or phenyl, each of which is substituted with one or more groups selected from the group consisting of a lower alkyl which may be substituted with one or more halogens, and a halogen.

(4) The pharmaceutical composition of any of (1) to (3), which is a thrombocytopenia treating agent.

(5) The pharmaceutical composition of any of (1) to (3), which is a c-Mpl ligand.

(6) A 2-acylaminothiazole derivative represented by the formula (III) or a pharmaceutically acceptable salt thereof.



[Symbols in the formula have the following meanings.

B: a group represented by A according to claim 1.

R⁴: a group represented by R¹ according to claim 1.

R⁵: a group represented by R² according to claim 1.

R⁶: a group represented by R³ according to claim 1, provided that unsubstituted phenyl and indole which may be substituted are excluded.]

(7) The compound of (6), wherein B is methylene.

(8) The compound of (7), wherein R⁵ is thienyl or phenyl, each of which is substituted with one or more groups selected from the group consisting of a lower alkyl which may be substituted with one or more halogens, and a halogen.

5 (9) The compound of (8), wherein R⁶ is pyridyl which may be substituted, or phenyl which is substituted.

(10) The compounds of (8), wherein R⁶ is pyridin-3-yl whose 5-position is substituted with a group selected from the group consisting of chloro and fluoro, and whose 6-
10 position is substituted, or phenyl whose 3-position is substituted with a group selected from the group consisting of chloro and fluoro, whose 5-position is substituted with a group selected from the group consisting of -H, chloro and fluoro, and whose 4-position is substituted.

15 (11) Compounds selected from the group consisting of compound group X and compound group Y, preferably compound group X, among the compounds of (6).

Here, "compound group X" is a compound group consisting of

20 1-{3-chloro-5-[(4-(4-chlorothiophen-2-yl)-5-
{[cyclobutyl(methyl)amino]methyl}thiazol-2-yl)carbamoyl]-2-
pyridyl}piperidine-4-carboxylic acid,

1-(5-{[5-{[butyl(methyl)amino]methyl}-4-(4-
chlorothiophen-2-yl)thiazol-2-yl]carbamoyl}-3-chloro-2-
25 pyridyl)piperidin-4-carboxylic acid,

1-{5-[(4-(4-chlorothiophen-2-yl)-5-{[(2R)-2-methylpyrrolidin-1-yl]methyl}thiazol-2-yl)carbamoyl]-3-fluoro-2-pyridyl}piperidin-4-carboxylic acid,

5 1-{3-chloro-5-[(4-(4-chlorothiophen-2-yl)-5-{[(2S)-2-methylpyrrolidin-1-yl]methyl}thiazol-2-yl)carbamoyl]-2-pyridyl}piperidine-4-carboxylic acid,

1-(3-chloro-5-{[4-(4-chlorothiophen-2-yl)-5-(dimethylaminomethyl)thiazol-2-yl]carbamoyl}-2-pyridyl)piperidine-4-carboxylic acid,

10 1-{3-chloro-5-[(4-(4-chlorothiophen-2-yl)-5-{[isopropyl(methyl)amino]methyl}thiazol-2-yl)carbamoyl]-2-pyridyl}piperidine-4-carboxylic acid,

4-[(3-chloro-5-[(4-(4-chlorothiophen-2-yl)-5-{[isopropyl(methyl)amino]methyl}thiazol-2-yl)carbamoyl]-2-pyridyl)(methyl)amino]butyric acid,

15 1-{3-chloro-5-[(4-(4-chlorothiophen-2-yl)-5-{[(3S)-3-methylpyrrolidin-1-yl]methyl}thiazol-2-yl)carbamoyl]-2-pyridyl}piperidine-4-carboxylic acid,

20 1-{3-chloro-5-[(4-(4-chlorothiophen-2-yl)-5-{[[2S)-2-methoxypropyl](methyl)amino]methyl}thiazol-2-yl)carbamoyl]-2-pyridyl}piperidine-4-carboxylic acid,

N-[5-{[butyl(methyl)amino]methyl}-4-(4-chlorothiophen-2-yl)thiazol-2-yl]-5-chloro-6-[(3-hydroxypropyl)amino]nicotinamide,

N-[5-{[butyl(methyl)amino]methyl}-4-(4-chlorothiophen-2-yl)thiazol-2-yl]-5-chloro-6-(3-oxopiperazin-1-yl)nicotinamide and

N-[5-{[butyl(methyl)amino]methyl}-4-(4-chlorothiophen-2-yl)thiazol-2-yl]-5-chloro-6-[4-(hydroxymethyl)piperidino]nicotinamide, and

pharmaceutically acceptable salts thereof, and

"compound group Y" is a compound group consisting of

1-{3-chloro-5-[(4-(4-chlorothiophen-2-yl)-5-{[(2R)-2-methylpyrrolidin-1-yl]methyl}thiazol-2-yl)carbamoyl]-2-pyridyl}piperidine-4-carboxylic acid,

4-[(3-chloro-5-[(4-(4-chlorothiophen-2-yl)-5-{[(2R)-2-methylpyrrolidin-1-yl]methyl}thiazol-2-yl)carbamoyl]-2-pyridyl)(methyl)amino]butyric acid,

4-[(3-chloro-5-[(4-(4-chlorothiophen-2-yl)-5-{[(2S)-2-methylpyrrolidin-1-yl]methyl}thiazol-2-yl)carbamoyl]-2-pyridyl)(methyl)amino]butyric acid,

1-{5-[(4-(4-chlorothiophen-2-yl)-5-{[(2S)-2-methylpyrrolidin-1-yl]methyl}thiazol-2-yl)carbamoyl]-3-fluoro-2-pyridyl}piperidine-4-carboxylic acid,

(1-{3-chloro-5-[(4-(4-chlorothiophen-2-yl)-5-{[(2R)-2-methylpyrrolidin-1-yl]methyl}thiazol-2-yl)carbamoyl]-2-pyridyl}azetidin-3-yl)acetic acid,

(1-{3-chloro-5-[(4-(4-chlorothiophen-2-yl)-5-{[(2S)-2-methylpyrrolidin-1-yl]methyl}thiazol-2-yl)carbamoyl]-2-pyridyl}azetidin-3-yl)acetic acid,

1-(3-chloro-5-([5-([isopropyl(methyl)amino)methyl]-4-(4-methylthiophen-2-yl)thiazol-2-yl]carbamoyl)-2-pyridyl)piperidine-4-carboxylic acid,

1-{3-chloro-5-[(4-(4-chlorothiophen-2-yl)-5-([(3R)-3-methylpyrrolidin-1-yl]methyl)thiazol-2-yl)carbamoyl]-2-pyridyl}piperidine-4-carboxylic acid,

1-{3-chloro-5-[(4-(4-chlorothiophen-2-yl)-5-([(2R)-2-methoxypropyl](methyl)amino)methyl)thiazol-2-yl)carbamoyl]-2-pyridyl}piperidine-4-carboxylic acid,

1-(5-([5-(azepan-1-ylmethyl)-4-(4-chlorothiophen-2-yl)thiazol-2-yl]carbamoyl)-3-chloro-2-pyridyl)piperidine-4-carboxylic acid,

1-{3-chloro-5-[(4-(4-chlorothiophen-2-yl)-5-[(2-methoxyethyl)(methyl)amino)methyl]thiazol-2-yl)carbamoyl]-2-pyridyl}piperidine-4-carboxylic acid,

1-(5-([5-azocan-1-ylmethyl)-4-(4-chlorothiophen-2-yl)thiazole-2-yl]carbamoyl)-3-chloro-2-pyridyl)piperidine-4-carboxylic acid,

1-{3-chloro-5-[(4-(4-chlorothiophen-2-yl)-5-[(cyclohexyl(methyl)amino)methyl]thiazol-2-yl)carbamoyl]-2-pyridyl}piperidine-4-carboxylic acid and

1-{3-chloro-5-[(4-(4-chlorothiophen-2-yl)-5-[(cyclopropyl(methyl)amino)methyl]thiazol-2-yl)carbamoyl]-2-pyridyl}piperidine-4-carboxylic acid, and

pharmaceutically acceptable salts thereof.

(12) A pharmaceutical composition comprising the compound according to any of claim 6 to 10 as an active ingredient.

(13) The pharmaceutical composition according to claim 11, which is a platelet increasing agent.

(14) The pharmaceutical composition according to claim 11, which is a thrombocytopenia treating agent.

(15) The pharmaceutical composition according to claim 11, which is a c-Mpl ligand.

A in the compounds represented by formula (I) and B in the compounds represented by formula (III) are preferably methylene.

R^1 in the compounds represented by formula (I) and R^4 in the compounds represented by formula (III) are preferably a group represented by formula (II) in which R^{11} is lower alkyl and R^{12} is lower alkyl or cycloalkyl which may be substituted respectively, or cyclic amino which may be substituted with lower alkyl; more preferably a group represented by formula (II) in which R^{11} is methyl and R^{12} is lower alkyl or cycloalkyl which may be substituted respectively, or cyclic amino which may be substituted with methyl.

R^2 in the compounds represented by formula (I) and R^5 in the compounds represented by formula (III) are preferably thienyl which may be substituted; more preferably thienyl substituted with one or more substituents selected from the

group consisting of lower alkyl which may be substituted with one or more halogens, and halogen; further preferably thienyl substituted with one or more groups selected from the group consisting of chloro and methyl; especially preferably 4-chlorothiophen-2-yl or 4-methylthiophen-2-yl. In another embodiment, R^2 in the compounds represented by formula (I) and R^5 in the compounds represented by formula (III) can be preferably phenyl which may be substituted; more preferably phenyl substituted with one or more groups selected from the group consisting of lower alkyl which may be substituted with one or more halogens, and halogen; further preferably phenyl substituted with one or more groups selected from the group consisting of trifluoromethyl, chloro and fluoro; especially preferably 3-trifluoromethylphenyl, 4-fluorophenyl or 3-chlorophenyl.

R^3 in the compounds represented by formula (I) and R^6 in the compounds represented by formula (III) are preferably pyridyl which may be substituted; more preferably pyridyl substituted with at least one halogen; more preferably pyridin-3-yl whose 5-position is substituted with a group selected from the member consisting of chloro and fluoro and whose 6-position is substituted. Of these, preferable is pyridin-3-yl whose 6-position is substituted with a group selected from the group consisting of piperidin-1-yl or piperazin-1-yl, each of which may be substituted with one or more groups selected from the group consisting of lower

alkyl substituted with substituent group W, substituent
group W and oxo, -O-lower alkyl, -NH-lower alkyl or -N(lower
alkyl)-lower alkyl which may be substituted with one or more
groups selected from substituent group W respectively, and
5 whose 5-position is substituted with a group selected from
the member consisting of chloro and fluoro.

Here, "substituent group W" indicates a group
consisting of -OH, -O-R^z, -OCO-R^z, carboxyl, -CO₂-R^z, -CO-R^z
and carbamoyl which may be substituted with one or two R^zs
10 (when carbamoyl is substituted with two R^zs, they may be the
same or different), cyano, amino which may be substituted
with one or two R^zs (when amino is substituted with two R^zs,
they may be the same or different), -NHCO-R^z, -NHCO₂-R^z,
sulfamoyl which may be substituted with one or two R^zs (when
15 sulfamoyl is substituted with two R^zs, they may be the same
or different), -SO₃H, -P(O)(OH)₂, -P(O)(OH)(OR^z),
-P(O)(OR^z)₂, aromatic heterocycle, non-aromatic heterocycle
and R^z. "R^z" represents lower alkyl, cycloalkyl or non-
aromatic heterocycle, each of which may be substituted with
20 one or more groups selected from the group consisting of
-OH, -O-lower alkyl (this lower alkyl may be substituted
with one or more groups selected from the member consisting
of -OH, -O-lower alkyl and amino), -OCO-lower alkyl,
carboxyl, -CO₂-lower alkyl, -CO-lower alkyl, carbamoyl which
25 may be substituted with one or two lower alkyls (when
carbamoyl is substituted with two lower alkyls, they may be

the same or different), cyano, amino which may be substituted with one or two lower alkyls (when amino is substituted with two lower alkyls, they may be the same or different), -NHCO-lower alkyl, -NHSO₂-lower alkyl, sulfamoyl which may be substituted with one or two lower alkyls (when sulfamoyl is substituted with two lower alkyls, they may be the same or different), -SO₃H, -P(O)(OH)₂, -P(O)(OH)(O-lower alkyl), -P(O)(O-lower alkyl)₂, aromatic heterocycle, non-aromatic heterocycle and halogen (this applies to the following).

In another embodiment, R³ in the compounds represented by formula (I) and R⁶ in the compounds represented by formula (III) can be preferably phenyl which may be substituted; more preferably phenyl substituted with at least one halogen; further preferably phenyl whose 3-position is substituted with a group selected from the member consisting of chloro and fluoro, whose 5-position is substituted with a group selected from the member consisting of -H, chloro and fluoro and whose 4-position is substituted. Of these, preferable is phenyl whose 4-position is substituted with a group selected from the group consisting of piperidin-1-yl or piperazin-1-yl, each of which may be substituted with one or more groups selected from the member consisting of lower alkyl substituted with substituent group W, substituent group W and oxo, -O-lower alkyl, -NH-lower alkyl or -N(lower alkyl)-lower alkyl which

may be substituted with one or more groups selected from
substituent group W respectively, and whose 3-position is
substituted with a group selected from the member consisting
of chloro and fluoro, and whose 5-position is substituted
5 with a group selected from the member consisting of -H,
chloro and fluoro.

In R^{11} , "when A represents methylene, R^{11} may be
present as methylene which is bridged to thienyl or phenyl
represented by R^2 " specifically means, for example, a
10 partial structure of compounds shown in Table 30.

In R^{11} , "when A represents methylene, R^{11} may be
present as a lower alkylene which may be substituted and
which forms a ring closed at the methylene represented by A"
specifically means, for example, a partial structure of
15 compounds shown in Table 33.

The compounds of the present invention are 2-
acylaminothiazole derivatives whose 2-position is
substituted with an acylamino group and whose 5-position is
substituted with lower alkyl substituted with a nitrogen
20 atom, in which point the characteristic feature of a
chemical structure lies. The compounds of the present
invention exhibit a human c-mpl-Ba/F3 cell growth activity,
an activity of accelerating division of human CD34⁺ cells to
megakaryocytes and a good oral activity in a mouse oral
25 administration test. Consequently, the compounds have a

pharmacological property in that they exhibit a platelet increasing function.

The compounds of the present invention are further described below.

5 In the present specification, the word "lower" means a linear or branched carbon chain having from 1 to 6 carbon atoms unless otherwise instructed.

 Accordingly, "lower alkyl" indicates C₁₋₆ alkyl. Specific examples thereof include methyl, ethyl, propyl,
10 isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, neopentyl, hexyl and the like. Methyl, ethyl, propyl and isopropyl, which are C₁₋₃ alkyl, are preferable.

 "Lower alkylene" is a divalent group of C₁₋₆ alkyl. Methylene, ethylene, trimethylene, methylethylene,
15 tetramethylene, dimethylmethylene and dimethylethylene, which are C₁₋₄ alkylene, are preferable. Methylene and ethylene are more preferable, and methylene is especially preferable.

 "Cycloalkyl" means a C₃₋₈ carbon ring, and it may
20 partially have one or more unsaturated bonds. Accordingly, specific examples thereof can include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclooctyl, cyclobutenyl, cyclohexenyl, cyclooctadienyl and the like.

 "Aryl" means a C₆₋₁₄ monocyclic to tricyclic aromatic
25 ring. Phenyl and naphthyl are preferable, and phenyl is more preferable.

"Cyclic amino" means a monovalent group of a 3- to 8-membered non-aromatic cyclic amine which has at least one nitrogen atom and may have further one or more hetero atoms selected from the member consisting of nitrogen, oxygen and sulfur, provided when plural hetero atoms are provided, they may be the same or different and at least one nitrogen atom has a bonding site. Specific examples thereof can include monovalent groups of azetidine, pyrrolidine, piperidine, azepane, azocane, azonane, azecane, piperazine, homopiperazine, morpholine and thiomorpholine, and the like.

"Non-aromatic heterocycle" means a monovalent group of a non-aromatic heterocycle having one or more hetero atoms selected from the member consisting of nitrogen, oxygen and sulfur, provided when plural hetero atoms are provided, they may be the same or different. Specific examples thereof can include monovalent groups of tetrahydrofuran, tetrahydropyran, tetrahydrothiofuran, tetrahydrothiopyran, oxetane, azetidine, pyrrolidine, piperidine, azepane, piperazine, homopiperazine, morpholine and thiomorpholine, and the like.

"Aromatic heterocycle" means a monovalent group of a 5- or 6-membered aromatic heterocycle having one or more hetero atoms selected from the member consisting of nitrogen, oxygen and sulfur, provided plural hetero atoms are provided, they may be the same or different, or the heterocycle which is partially hydrogenated. Specific

examples thereof can include monovalent groups of pyridine, pyrazine, pyrimidine, pyridazine, pyrrole, imidazole, oxazole, thiazole, thiophene and furan. These heterocycles may be condensed with a benzene ring.

5 Examples of "halogen" include fluoro, chloro, bromo and iodo, and fluoro and chloro are preferable.

 In the present specification, with respect to permissible substituents of the terms "which may be substituted" and "substituted", any substituents are
10 available so long as they are ordinarily used as substituents of the respective groups. One or more of these substituents may be present in the respective groups.

 Regarding permissible substituents in "cyclic amino which may be substituted" in R^1 and R^4 , "cycloalkyl which
15 may be substituted" in R^{11} , "cycloalkyl or non-aromatic heterocycle which may be substituted respectively" in R^{12} and "thienyl or phenyl which may be substituted respectively" in R^2 and R^5 , the following groups (a) to (h) are listed.

20 (a) halogen;

 (b) $-OH$, $-O-R^Z$, $-O-aryl$, $-OCO-R^Z$, $oxo(=O)$;

 (c) $-SH$, $-S-R^Z$, $-S-aryl$, $-SO-R^Z$, $-SO-aryl$, $-SO_2-R^Z$, $-SO_2-aryl$, sulfamoyl which may be substituted with one or two R^Z s;

25 (d) amino which may be substituted with one or two R^Z s, $-NHCO-R^Z$, $-NHCO-aryl$, $-HNCO_2-R^Z$, $-NHCONH_2$, $NHSO_2-R^Z$,

-NHSO₂-aryl, -NHSO₂NH₂, nitro;

(e) -CHO, -CO-R², -CO₂H, -CO₂-R², carbamoyl which may be substituted with one or two R²s, cyano;

(f) aryl or cycloalkyl, each of which may be substituted with one or more groups selected from the group consisting of -OH, -O-lower alkyl, amino which may be substituted with one or two lower alkyls, halogen and R²;

(g) aromatic heterocycle or non-aromatic heterocycle, each of which may be substituted with one or more groups selected from the group consisting of -OH, -O-lower alkyl, amino which may be substituted with one or two lower alkyls, halogen and R²; and

(h) lower alkyl which may be substituted with one or more groups selected from substituents shown in (a) to (g).

Permissible substituents in "lower alkyl which may be substituted" and "lower alkylene which may be substituted" in R¹¹ and "lower alkyl which may be substituted" in R¹² include the groups listed in (a) to (g).

Examples of permissible substituents in "aromatic heterocycle, aryl or cyclic amino which may be substituted respectively" in R³ and R⁶ can include halogen, lower alkyl which may be substituted with one or more halogens, -OH, -O-R², oxo, amino which may be substituted with one or two R²s and a group represented by formula (III). When the substituent is amino substituted with two R²s, the two R²s may be the same or different.



[Symbols in the formula have the following meanings.

X: cyclic aminediyl which may be substituted with one
5 or more groups selected from the group consisting of -OH,
-O-lower alkyl, halogen, oxo and R².

Y: single bond, -O-lower alkylene or -N(lower alkyl)-
lower alkylene.

Z: substituent group W, -cyclic aminediyl-substituent
10 group W or -CO-cyclic aminediyl-substituent group W.]

"Cyclic aminediyl" means a divalent group of 3- to 8-
membered non-aromatic cyclic amine which has at least one
nitrogen atom and may have further one or more hetero atoms
selected from the member consisting of nitrogen, oxygen and
15 sulfur, provided when plural hetero atoms are provided, they
may be the same or different and at least one nitrogen atom
has a bonding site. Specific examples thereof can include
divalent groups of azetidine, pyrrolidine, piperidine,
azepane, azocane, azonane, azecane, piperazine,
20 homopiperazine, morpholine and thiomorpholine.

The compounds represented by formula (I) which are an
active ingredient of medications of the present invention or
the compounds represented by formula (III) which are
compounds of the present invention sometimes contain an
25 asymmetric carbon atom according to the type of the
substituent, and optical isomers may be present based on

this. The present invention includes all of a mixture of these optical isomers and optical isomers which are isolated. Further, with respect to the compounds according to the present invention, tautomers sometimes exist. The present invention includes tautomers which are separated or a mixture thereof. Still further, the present invention includes labeled compounds, namely the compounds of the present invention with one or more atoms substituted with a radioactive isotope or a nonradioactive isotope.

The compounds according to the present invention are sometimes formed into salts which are included in the present invention so long as they are pharmaceutically acceptable salts. Specific examples thereof include acid addition salts with inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid and phosphoric acid or organic acids such as formic acid, acetic acid, propionic acid, oxalic acid, malonic acid, succinic acid, fumaric acid, maleic acid, lactic acid, malic acid, tartaric acid, citric acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, aspartic acid and glutamic acid, salts with inorganic bases containing metals such as sodium, potassium, calcium and magnesium or organic bases such as methylamine, ethylamine, ethanolamine, lysine and ornithine, ammonium salts and the like. The present invention also includes hydrates, solvates and polycrystalline substances of the

compounds of the present invention and the pharmaceutically acceptable salts thereof. The present invention also includes all of compounds which are converted to the compounds represented by formula (I) or (III) or the salts thereof by being metabolized in vivo, so-called prodrugs. Groups that form the prodrugs of the present invention include groups described in Prog. Med. 5:2157-2161 (1985) and groups described in Hirokawa Shoten, 1990, "Iyakuhin no Kaihatsu", vol. 7, Bunshi Shekkei pp. 163-198.

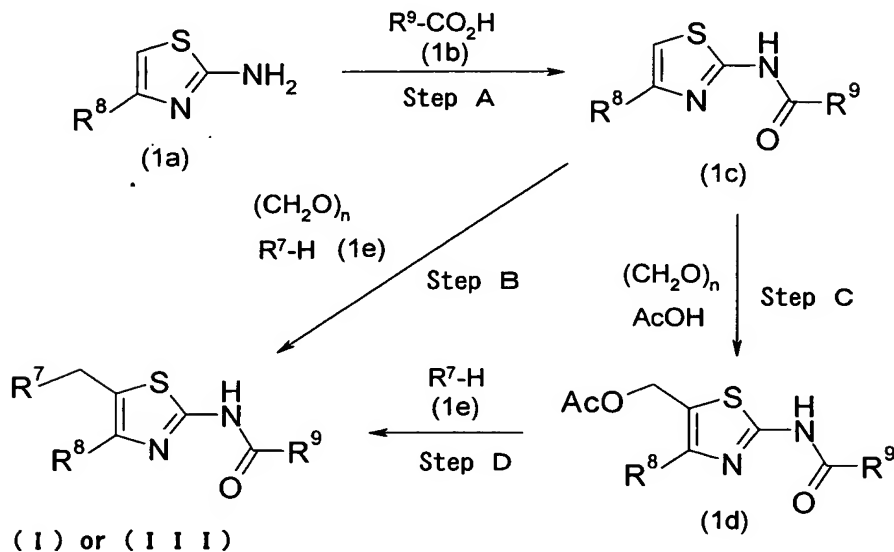
(Process)

The compounds and the pharmaceutically acceptable salts thereof according to the present invention can be produced by utilizing characteristics based on the basic structure or the types of the substituents and applying various known synthesis processes. Typical processes are described below. Some types of functional groups are substituted with appropriate protective groups, namely groups easily convertible to the very functional groups in the stage of starting materials or intermediates, which is sometimes effective in the production technique.

Thereafter, protective groups are removed, as required, to be able to obtain the desired compounds. Examples of such functional groups can include a hydroxyl group, a carboxyl group, an amino group and the like. Examples of the protective groups can include protective groups described in, for example, Green and Wuts, "Protective Groups in

Organic Synthesis (third edition)". These may properly be used according to reaction conditions.

(First process)



5

(wherein R^7 represents a group represented by the foregoing formula (II) in which R^{11} is H, lower alkyl which may be substituted or cycloalkyl which may be substituted or represents a cyclic amino group which may be substituted; and R^8 represents the foregoing group represented by R^2 or R^5 ; R^9 represents the foregoing group represented by R^3 or R^6 or a group which is convertible to R^3 or R^6 by a method which can ordinarily be employed by a skilled person. This applies to the following.)

15

This process is a process for producing a compound, among the compounds of the present invention represented by formula (I) or (III), in which A is methylene, R^1 and R^2 (or

R⁴ and R⁵) are not crosslinked, and R¹ or R⁴ and A are not ring-closed.

(Step A)

This step is a step in which compound (1c) is produced
5 by amidation of compound (1a) or its salt with compound (1b) or its reactive derivative in a usual manner and removing a protective group as required.

As the amidation in this step, amidation which can ordinarily be used by a skilled person is employable.

10 Especially, a method in which phosphorus oxychloride is used in a pyridine solvent, and a method in which a condensing agent such as 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (WSC·HCl), dicyclohexylcarbodiimide, carbonyldiimidazole, diphenylphosphorylazide or
15 diethylphosphorylcyanide is used in the presence of 1-hydroxybenzotriazole (HOBt) are advantageously used.

The reaction varies with reactive derivatives or a condensing agent used. Usually, the reaction is conducted in an organic solvent inactive to the reaction under
20 cooling, under cooling to room temperature or under room temperature to heating, examples of the organic solvent including halogenated hydrocarbons such as dichloromethane, dichloroethane and chloroform, aromatic hydrocarbons such as benzene, toluene and xylene, ethers such as ether and
25 tetrahydrofuran (THF), esters such as ethyl acetate (EtOAc),

acetonitrile, N,N-dimethylformamide (DMF), dimethyl sulfoxide (DMSO) and the like.

(Step B)

This step is a step in which compound (I) or (III) of
5 the present invention is produced by introducing an
aminomethyl group in the 5-position of thiazole of compound
(1c) using a Mannich reaction with compound (1e). A method
described in Alvertson, N. F.; J Am Chem Soc 1948, 70, 669
or Bhargava, P. N.; Sharma, S. C.; Bull Chem Soc Jpn 1965,
10 38, 909. or a method corresponding thereto can be employed.

(Step C, Step D)

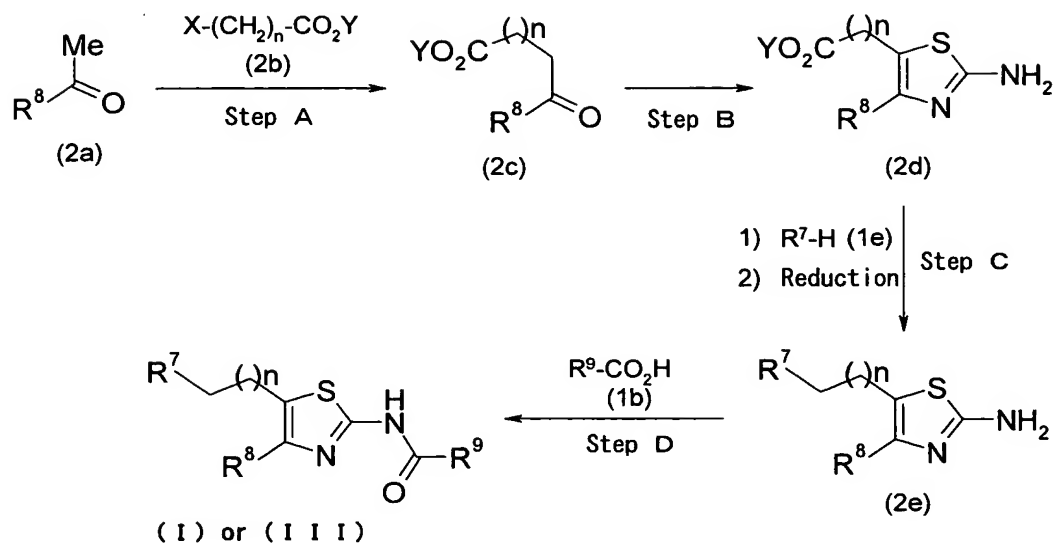
These steps are steps in which compound (I) or (III)
of the present invention is produced by introducing an
acetoxymethyl group in the 5-position of thiazole of
15 compound (1c) and then conducting a nucleophilic
substitution reaction with compound (1e) under a basic
condition.

The acetoxymethylation in step C can be conducted
under room temperature to heating or under room temperature
20 to reflux by reacting compound (1c) with a formaldehyde
aqueous solution or a p-formaldehyde in an acetic acid
solvent. The reaction may be conducted by adding acetic
acid in a solvent inactive to the reaction, such as
halogenated hydrocarbons, aromatic hydrocarbons or ethers
25 instead of an acetic acid solvent. In this case, a

reactivity tends to be decreased. Further, the reaction may be conducted by addition of acetic anhydride.

The nucleophilic substitution reaction in step D can be conducted by reacting compound (1d) with compound (1e) in
5 an organic solvent inactive to the reaction, such as halogenated hydrocarbons, aromatic hydrocarbons, ethers, esters, acetonitrile, DMF or DMSO in the presence of an organic base such as triethylamine or diisopropylethylamine and/or an inorganic base such as potassium carbonate, sodium
10 carbonate, cesium carbonate or sodium hydrogencarbonate. For acceleration of the reaction, a catalyst such as dimethylaminopyridine may be added. Instead of the organic base and/or the inorganic base, a larger amount of compound (1e) may be used. The reaction varies with the base used.
15 It can be conducted under cooling to room temperature, under room temperature to heating or under room temperature to reflux.

(Second process)



(wherein X represents a leaving group such as halogen; Y

5 represents lower alkyl; and n represents an integer of from 1 to 6. This applies to the following.)

This process is a process for producing a compound, among the compounds of the present invention represented by formula (I) or (III), in which A or B is lower alkylene except methylene, R^1 and R^2 or R^4 and R^5 are not crosslinked, and R^1 and A or R^4 and B are not ring-closed.

(Step A)

This step is a step in which compound (2c) is produced by condensing compound (2a) and compound (2b). A method described in HAND, E. S.; JOHNSON, S. C.; BAKER, D. C.; J Org Chem 1997, 62(5), 1348-1355 or a method corresponding thereto can be employed.

(Step B)

This step is a step in which the α -position of ketone in compound (2c) is halogenated and the compound is then reacted with thiourea to form a thiazole ring. A method
5 described in Org. Syn. Coll. Vol. II, 1943, 32-32., and Maruzen, 1992, "Dai 4 han Jikken Kagaku Koza 19", pp. 431-435, or a method corresponding thereto can be employed.

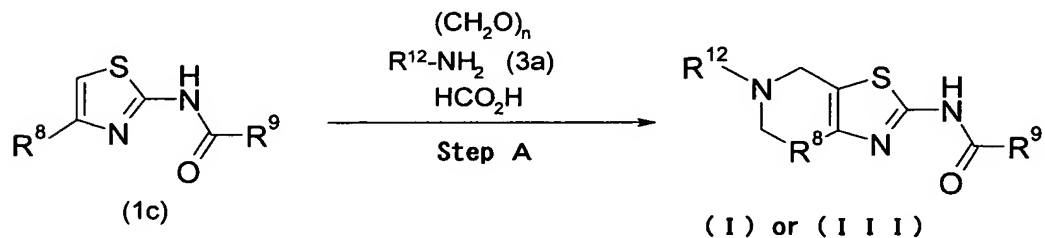
(Step C)

This step is a step in which compound (2d) or the
10 carboxylic acid compound subjected to hydrolysis as required is amidated according to step A in the first process and the amide bond is then converted to an aminomethylene bond by a reduction reaction. A method described in Maruzen, 1992, "Dai 4 han Jikken Kagaku Koza 26", pp. 227-228, or a method
15 corresponding thereto can be employed.

(Step D)

This step is a step in which compound (I) or (III) of the present invention is produced by amidation of compound (2e) with compound(1b). The step can be conducted according
20 to step A in the first process.

(Third process)



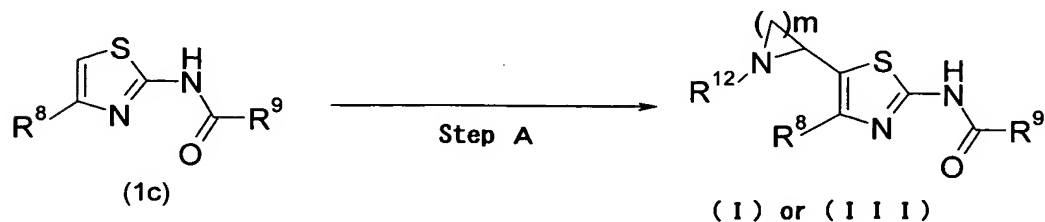
(wherein R^{12} represents the foregoing group. This applies to the following.)

This process is a process for producing a compound, among the compounds of the present invention represented by
5 formula (I) or (III), in which R^1 and R^2 (or R^4 and R^5) are crosslinked by R^{11} . R^{11} is present as methylene crosslinked on R^2 or R^5 when A or B is methylene and R^1 or R^4 is a group represented by formula (II) according to the foregoing definition.

10 (Step A)

This step is a step in which an aminomethyl group is introduced into the 5-position of thiazole of compound (1c) using a Mannich reaction with compound (1c) and phenyl or thienyl represented by R^2 nucleophilically attacks iminium
15 formed by the subsequent second-stage Mannich reaction to give a tricyclic compound, the compound of the present invention. The step can be conducted according to step B in the first process.

(Fourth process)



(wherein m represents an integer of from 1 to 6. This applies to the following.)

This process is a process for producing a compound, among the compounds of the present invention represented by formula (I) or (III), in which R^1 and A (or R^4 and B) are ring-closed by R^{11} . R^{11} is present as lower alkylene which
5 may be substituted and which is ring-closed on A or B when A or B is methylene and R^1 or R^4 is a group represented by formula (II) according to the foregoing definition.

(Step A)

This step can be conducted according to a method of
10 Van Tamelin, E. E.; Knapp, G. C.; J. Am. Chem. Soc., 77, 1860, 1955.

In the first to fourth processes, the next step can proceed by converting a group represented by R^9 to R^3 or R^6 in an appropriate time of the foregoing step. As to the
15 conversion method, for example, a method can be described in which in step A, 5,6-dichloropyridin-3-yl or 3,4,5-difluorophenyl is introduced as R^9 , and ipso substitution is conducted by a nucleophilic reaction in an appropriate time, for example, before step B, before step C or before step D
20 in the first process to convert the group to R^3 or R^6 , a partial structure of the compounds according to the present invention.

Further, some compounds represented by formula (I) or (III) may be produced from the compounds of the present
25 invention which have been obtained in the foregoing manner by arbitrarily combining steps that can ordinarily be

employed by a skilled person, such as known alkylation, acylation, substitution reaction, oxidation, reduction and hydrolysis.

The thus-produced compounds according to the present invention are isolated and purified either in free form or as salts thereof by undergoing salt-forming treatment in a usual manner. Isolation and purification are performed by ordinary chemical procedures such as extraction, concentration, distillation, crystallization, filtration, recrystallization and various chromatographies.

Various isomers can be isolated in a usual manner by utilizing a difference in physicochemical properties between isomers. For example, a racemic mixture can be introduced into optically pure isomers by a general racemic compound resolution method, for example, a method in which the mixture is formed into a diastereomer salt with a general optically active acid such as tartaric acid to conduct optical resolution. A diastereo-mixture can be separated by, for example, fractional crystallization or various chromatographies. An optically active compound can be produced using an appropriate optically active starting material.

Industrial Applicability

The compounds according to the present invention have an excellent platelet increasing function. Therefore, the

compounds according to the present invention are useful for treating and/or preventing various thrombocytopenias such as thrombocytopenia in anemia and myelodysplastic syndrome, thrombocytopenia caused by chemotherapy and radiotherapy of malignant tumor, thrombocytopenia in idiopathic thrombocytopenic purpura, thrombocytopenia in hepatic diseases and thrombocytopenia caused by HIV. When there is a possibility of causing thrombocytopenia by chemotherapy or radiotherapy, previous administration is also possible before conducting these therapies.

Pharmacological functions of the compounds according to the present invention were confirmed by the following tests.

(i) Human c-mpl-Ba/F3 cell growth test

In a 96-well microplate, 2×10^5 cells/ml of human c-mpl-Ba/F3 cells were cultured at 37°C in 10% fetal bovine serum-containing RPMI1640 medium (100 µl/well) containing each test compound at each concentration. After 24 hours from the start-up of culture, 10 µl/well of WST-1/1-methoxy PMS (cell counting kit, Dojin) was added. Immediately after addition and 2 hours after addition, absorbance of A450/A650 was measured with a microplate reader (Model 3350: Bio-Rad), and an increase in absorbance for 2 hours was defined as a growth activity of each test compound. The results are shown in Table 1.

Symbols in the table have the following meanings.

pot: Concentration of each test compound at which to accelerate cell growth by 30% of a maximum cell growth activity of compound A (compound A and rhTPO in rhTPO)

Efficacy: Maximum cell growth activity of each test compound when a maximum cell growth activity of compound A (compound A and rhTPO in rhTPO) is defined as 100%.

Compound A refers to a compound in Example 9 of the foregoing Patent Document 10.

10 (Table 1)

Human c-mpl-Ba/F3 cell growth activity

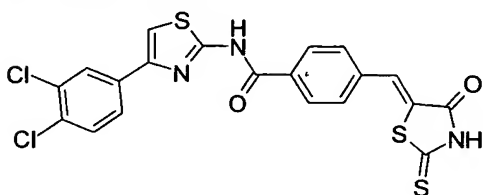
Test Compound	Pot [nM]	Efficacy [%]	Test Compound	Pot [nM]	Efficacy [%]
Example 65	4.3	114	Example 151	8.4	99
Example 71	2.0	110	Example 153	6.1	99
Example 84	4.2	103	Example 222	4.4	102
Example 85	3.3	107	Example 226	4.6	88
Example 90	2.0	94	Example 227	3.2	88
Example 100	2.9	117	Example 315	3.2	98
Example 101	3.1	108	Comparative Compound 1	4.4	101
Example 104	3.5	105	Comparative Compound 2	2.1	96
Example 106	2.1	112	Comparative Compound 3	6.9	96
Example 107	1.5	112	Comparative Compound 4	251	95
Example 109	3.9	95	Compound A	10	87
Example 111	6.0	87	rhTPO	0.012	100
Example 150	3.6	102			

In the table, Comparative Compound 1 is a compound of Compound No. A-1 in the foregoing Patent Document 7;

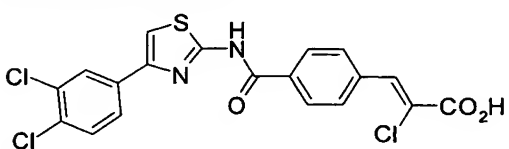
15 Comparative Compound 2 is a compound of Compound No. A-14 in

the foregoing Patent Document 8; Comparative Compound 3 is a compound of Compound No. J-14 in the foregoing Patent Document 8; and Comparative Compound 4 is a compound in Example 2 of the foregoing Patent Document 9. Structures of
 5 Comparative Compounds 1 to 4 and Compound A are shown below.

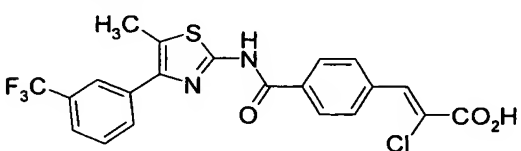
Comparative compound 1



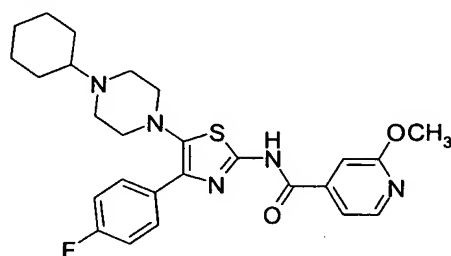
Comparative compound 2



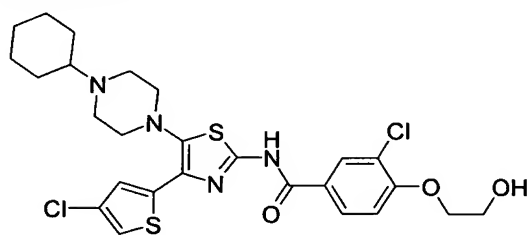
Comparative compound 3



Comparative compound 4



Compound A



From the foregoing results, the compounds of the
 10 present invention have been confirmed to have the Ba/F3 cell growth function mediated by human c-Mpl.

(ii) Test for measuring a function of accelerating
 formation of megakaryocytic colonies

Human CD34⁺ cells were cultured in a 2-well chamber
 15 slide in the presence of a test product at 37°C for from 10 to 14 days using MegaCultTM-C (StemCell Technologies). After

dehydration and fixation were conducted according to the attached manual, dying was conducted with an anti-glycoprotein IIb/IIIa antibody. The number of colonies for 1 well was counted by a microscope on condition that a population of 3 or more dyed megakaryocytes was one colony. An EC₃₀ value of each test compound was calculated from a dose curve.

Consequently, with respect to the EC₃₀ value of the compounds of the present invention, the compound in Example 71 is 20 nM, the compound in Example 100 34 nM, the compound in Example 104 36 nM, the compound in Example 106 23 nM, and the compound in Example 315 45 nM. It has been confirmed that the compounds of the present invention have the excellent function of accelerating formation of megakaryocytic colonies.

(iii) Mouse oral administration test

3 mg/kg or 10 mg/kg (100 mg/kg in Comparative Compounds 1 to 3) of a test compound dissolved or suspended in a 0.5% methylcellulose aqueous solution was orally administered to a male ICR mouse. After 2 hours from administration, a blood was sampled from the subabdominal large vein using 1/10-volume 3.8% sodium citrate as an anticoagulant. Centrifugation was performed at 12,000 rpm for 3 minutes. The resulting plasma was heated at 56°C for 30 minutes, and added to a system of the human c-mpl-Ba/F3 cell growth test described in (i) such that the final

concentration of the plasma reached 0.3%, 1% or 3% (10% in Comparative Compounds 1 to 3) to measure a cell growth activity. The cell growth activity (%) of each plasma was measured when the maximum cell growth activity of each test compound was defined as 100%.

(Table 2)

Human c-mpl-Ba/F3 cell growth activity of a plasma after oral administration

Test Compound	Dose [mg/kg p.o.]	Dilution rate [%]	Cell growth activity[%]
Example 65	3	3	≥80
Example 71	3	3	≥80
Example 84	3	1	≥80
Example 85	3	1	≥80
Example 90	3	0.3	≥80
Example 100	3	3	≥80
Example 101	3	1	76
Example 104	3	1	63
Example 106	3	1	63
Example 109	3	1	59
Example 150	3	0.3	28
Example 151	10	3	24
Example 153	10	3	29
Example 314	3	3	52
Comparative Compound 1	100	10	<10
Comparative Compound 2	100	10	<10
Comparative Compound 3	100	10	<10

Comparative Compounds 1 to 3 in the table are the same as Comparative Compounds 1 to 3 in the foregoing Table 1 respectively.

From the foregoing results, it has been confirmed that the compounds of the present invention have an oral activity in mice. Especially, it has been found that in the comparative compounds, the oral activity is little shown even "under a condition of 100 mg/kg - 10% dilution", whereas in the compounds of the present invention, the good oral activity is exhibited even "under a condition of a lower dose of 3 mg/kg or 10 mg/kg - higher dilution of 3% or less". This is quite unexpected, and is considered to have been achieved by introduction of lower alkylene having an amino group as a substituent in the 5-position of thiazole. In Comparative Compound 2 and Comparative Compound 3, the cell growth activity has been less than 10% also in the lower dose (10 mg/kg p.o.).

It has been confirmed that a platelet increasing activity is observed by administering the compound of the present invention to a mouse in which human platelet production has been identified after transplantation of human hematopoietic stem cells.

The medication of the present invention can be prepared by an ordinary method using at least one of the compounds represented by formula (I) or (III) according to the present invention as well as a carrier, an excipient and other additives for use in drugs which are commonly used in formulation. The administration may be any of oral administration with tablets, pills, capsules, granules,

powders, liquid preparations or the like and parenteral administration with injections such as intravenous injection and intramuscular injection, administration with suppositories, transnasal administration, permucosal administration or percutaneous administration.

As a solid composition for oral administration according to the present invention, tablets, powders, granules and the like are used. In such a solid composition, one or more active substances are mixed with at least one inactive diluent such as lactose, mannitol, glucose, hydroxypropylcellulose, microcrystalline cellulose, starch, polyvinyl pyrrolidone or magnesium aluminate metasilicate. The composition may contain, according to a usual method, additives other than an inactive diluent, for example, a lubricant such as magnesium stearate, a disintegrant such as calmellose calcium, a stabilizer and a solubilizer. Tablets or pills may be coated, as required, with a sugar coating such as sucrose, gelatin, hydroxypropylcellulose or hydroxypropylmethylcellulose phthalate, or a gastric or enteric film.

A liquid composition for oral administration contains an emulsifying agent, a liquor, a suspending agent, a syrup, an elixir and the like which are pharmaceutically acceptable, and an inactive diluent which is generally used, such as purified water or ethanol (EtOH). This composition may contain, in addition to the inactive diluent, aids such

as a wetting agent and a suspending agent, a sweetener, a flavor, an aromatic and a preservative.

An injection for parenteral administration contains a liquor and a suspending agent which are sterile and aqueous
5 or non-aqueous and an emulsifying agent. Examples of the aqueous liquor and suspending agent include distilled water for injection and a physiological saline solution. Examples of the non-aqueous liquor and suspending agent include vegetable oils such as propylene glycol, polyethylene glycol
10 and olive oil, alcohols such as EtOH, polysorbate 80 and the like. Such a composition may further contain aids such as a preservative, a wetting agent, an emulsifying agent, a dispersing agent, a stabilizer and a solubilizing agent. These are sterilized by filtration through a bacteria
15 holding filter, incorporation of a disinfectant or irradiation. Further, these may be formed into a sterile solid composition which is used by being dissolved in sterile water or a sterile solvent for injection before use.

In case of oral administration, a dose for one day is
20 generally from approximately 0.0001 to 50 mg/kg, preferably from approximately 0.001 to 10 mg/kg, more preferably from 0.01 to 1 mg/kg per body weight. This is administered either once or in divided portions, from 2 to 4 times. In case of intravenous administration, a dose for one day is
25 from approximately 0.0001 to 1 mg/kg, preferably from approximately 0.0001 to 0.1 mg/kg. This is administered

either once or plural times per day. The dose is properly determined according to each case in consideration of the condition, the age, the sex and the like of patients.

5 Best Mode for Carrying Out the Invention

The present invention is specifically described below by referring to Examples. However, the invention is not limited at all by these Examples. Starting compounds used in Examples include novel substances, and processes for
10 producing such starting compounds from known products are described as Reference Examples.

Reference Example 1

Potassium carbonate and allyl bromide were added to a
15 DMF solution of 3,4,5-trifluorobenzoic acid, and the mixture was stirred overnight to obtain a crude allyl ester. Potassium carbonate was added to a DMF solution of the crude allyl ester and ethyl isonipecotate, and the mixture was stirred overnight at room temperature to obtain a piperidine
20 substitution product. Morpholine and tetrakis(triphenylphosphine)palladium (catalytic amount) were added to a THF solution of the piperidine substitution product, and the mixture was stirred at 60°C for 2 hours and at room temperature for 4 days. After the solvent was
25 distilled off, ether and EtOAc were added, and the mixture was washed 10 times with an saturated sodium

hydrogencarbonate aqueous solution. Conc. hydrochloric acid was added to the collected aqueous layer, and the resulting precipitate was collected by filtration to obtain 4-[4-(ethoxycarbonyl)piperidin-1-yl]-3,5-difluorobenzoic acid.

5

Reference Example 2

Potassium carbonate and 3-(tert-butyltrimethylsilyloxy)propyl bromide were added to a DMF solution of ethyl 3-chloro-5-fluoro-4-hydroxybenzoate, and the mixture was stirred at 50°C to obtain ethyl 4-[3-(tert-butyltrimethylsilyloxy)propoxy]-3-chloro-5-fluorobenzoate.

10

Compounds in Reference Examples 3 and 4 shown in Table 3 were produced in the same manner as in Reference Example 2 using the corresponding starting materials respectively.

15

Reference Example 5

Anhydrous piperazine was added to a THF solution of methyl 3,4-difluorobenzoate, and the mixture was stirred at 60°C for 18 hours to obtain methyl 3-fluoro-4-piperazin-1-ylbenzoate.

20

Reference Example 6

Di-tert-butyl dicarbonate and 4-dimethylaminopyridine were added to a 1,2-dichloroethane solution of the compound in Reference Example 5, and the mixture was stirred at room

25

temperature for 10 minutes to obtain tert-butyl 4-[2-fluoro-4-(methoxycarbonyl)phenyl]piperazine-1-carboxylate.

Reference Example 7

N-chlorosuccinimide was added to a DMF solution of the compound in Reference Example 6, and the mixture was stirred at room temperature for 3 hours to obtain tert-butyl 4-[2-chloro-6-fluoro-4-(methoxycarbonyl)phenyl]piperazine-1-carboxylate.

Reference Example 8

A 1M NaOH aqueous solution (aq) was added to an MeOH-THF mixed solution of the compound in Reference Example 2, and the mixture was stirred at room temperature for 16 hours to obtain 4-[3-(tert-butyldimethylsilyloxy)propoxy]-3-chloro-5-fluorobenzoic acid.

Compounds in Reference Examples 9 to 11 shown in Table 3 were produced in the same manner as in Reference Example 8 using the corresponding starting materials respectively.

Reference Example 12

Thionyl chloride was added to an MeOH solution of the compound in Reference Example 11, and the mixture was stirred at room temperature for 22 hours to obtain 4-[3-(methoxycarbonyl)propoxy]-3-fluorobenzoic acid.

Symbols in the table have the following meanings (this applies to the following).

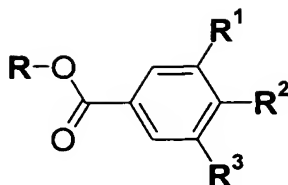
Rf: Reference Example No.

Data: Physical data (MS:FAB-MS(M+H)⁺; MN:FAB-MS(M-H)⁻;

5 MM:FAB-MS(M)⁺),

R, R¹, R², R³, R⁴, X, Y: Substituents in the general formulas (Me: methyl, Et: ethyl, iPr: isopropyl, cPr: cyclopropyl, nBu: normal butyl, iBu: isobutyl, tBu: tertiary butyl, Ph: phenyl, Py: pyridyl, Boc: tert-butyloxycarbonyl, 10 The:thienyl, azet: azetidin-1-yl, pyrr: pyrrolidin-1-yl, pipe: piperidin-1-yl, pipa: piperazin-1-yl, mor: morpholin-4-yl, TBS: tertiary butyldimethylsilyl, di:di. The number before the substituent indicates a substitution position. Accordingly, for example, 3,5-diF-4-(4-EtO₂C-pipe)Ph refers 15 to 3,5-difluoro-4-(4-ethoxycarbonylpiperidin-1-yl)phenyl, and 4-Me-2-The refers to 4-methylthiophen-2-yl).

(Table 3)



Rf	R¹, R², R³, R				Data
1	R¹= F,	R²= 4-EtO₂C-pipe,	R³= F,	R= H	MS;314.
2	R¹= Cl,	R²= TBSO(CH₂)₃O-,	R³= F,	R= Et	MS;391.
3	R¹= OMe,	R²= TBSO(CH₂)₂O-,	R³= H,	R= Et	MS;355.
4	R¹= F,	R²= EtO₂C(CH₂)₃O-,	R³= H,	R= Me	MS;285.
5	R¹= F,	R²= pipa,	R³= H,	R= Me	MS;239.
6	R¹= F,	R²= 4-Boc-pipa,	R³= H,	R= Me	MS;339.
7	R¹= Cl,	R²= 4-Boc-pipa,	R³= F,	R= Me	MS;373.
8	R¹= Cl,	R²= TBSO(CH₂)₃O-,	R³= F,	R= H	MS;363.
9	R¹= Cl,	R²= 4-Boc-pipa,	R³= F,	R= H	MS;359.
10	R¹= OMe,	R²= TBSO(CH₂)₂O-,	R³= H,	R= H	MS;327.
11	R¹= F,	R²= HO₂C(CH₂)₃O-,	R³= H,	R= H	MN;241.
12	R¹= F,	R²= MeO₂C(CH₂)₃O-,	R³= H,	R= H	MS;257.

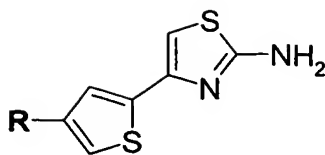
Reference Example 13

5 Bromine was added to an ether solution of 4-chloro-2-acetylthiophene under ice cooling, and the mixture was stirred at room temperature for 2 hours to obtain a brominated compound. Thiourea was added to an EtOH solution of the brominated compound at room temperature, and the mixture was stirred overnight at 80°C to obtain 2-amino-4-(4-chlorothiophen-2-yl)thiazole.

A compound in Reference Example 14 shown in Table 4 was obtained in the same manner as in Reference Example 13 using the corresponding starting material.

15

(Table 4)



Rf	R	Data
13	Cl	MS;217.
14	Me	MS;197.

5

Reference Example 15

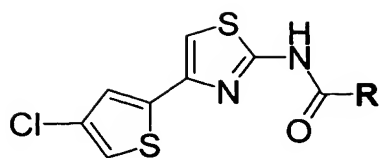
Phosphorus oxychloride was added to a pyridine suspension of the compound in Reference Example 13 and 5,6-dichloronicotinic acid. The temperature was gradually raised, and the mixture was stirred overnight at room temperature to obtain 5,6-dichloro-N-[4-(4-chlorothiophen-2-yl)thiazol-2-yl]nicotinamide.

10

Compounds in Reference Examples 16 to 22 shown in Table 5 were produced in the same manner as in Reference Example 15 using the corresponding starting materials.

15

(Table 5)



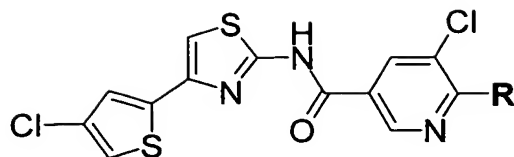
Rf	R	Data
15	5,6-diCl-3-Py	MS;390.
16	2-MeO-4-Py	MS;352.
17	3,5-diF-4-(4-EtO ₂ C-pipe)Ph	MS;512.
18	3-Cl-5-F-4-TBSO(CH ₂) ₃ O-Ph	MS;561.
19	3-Cl-5-F-4-(4-Boc-pipa)Ph	MS;557.
20	3-Cl-4-MeOCH ₂ O-Ph	MS;415.
21	3-MeO-4-TBSO(CH ₂) ₂ O-Ph	MS;624.
22	3-F-4-MeO ₂ C(CH ₂) ₃ O-Ph	MS;455.

Reference Example 23

5 Pyridine, triethylamine and ethyl isonipecotate were added to the compound in Reference Example 15, and the mixture was stirred at 70°C for 16 hours to obtain ethyl 1-(3-chloro-5-{[4-(4-chlorothiophen-2-yl)thiazol-2-yl]carbamoyl}-2-pyridyl)piperidine-4-carboxylate.

10 Compounds in Reference Examples 24 to 31 shown in Table 6 were produced in the same manner as in Reference Example 23 using the corresponding starting materials respectively.

(Table 6)



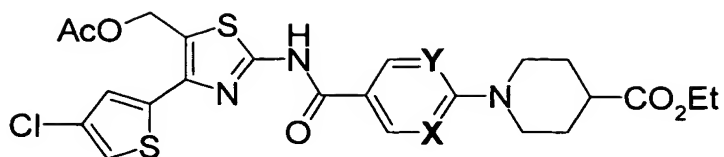
Rf	R	Data
23	4-EtO ₂ C-pipe	MS;511.
24	3-EtO ₂ C-pipe	MS;511.
25	3-MeO ₂ C-pyrr	MS;483.
26	(R)-3-MeO ₂ CCH ₂ O-pyrr	MS;513.
27	4-EtO ₂ CCH ₂ -pipe	MS;525.
28	2-EtO ₂ C-mor	MS;513.
29	(S)-3-MeO ₂ C-pyrr	MS;483.
30	3-EtO ₂ C-azet	MS;483.
31	4-tBuO ₂ CCH ₂ O-pipe	MS;569.

Reference Example 32

5 Acetic acid and a formaldehyde aqueous solution (36%) were added to the compound in Reference Example 23, and the mixture was stirred overnight at 100°C to obtain ethyl 1-(5-acetoxymethyl-4-(4-chlorothiophen-2-yl)thiazol-2-yl)carbamoyl)-3-chloro-2-pyridyl)piperidine-4-carboxylate.

10 A compound in Reference Example 33 shown in Table 7 was produced in the same manner as in Reference Example 32 using the corresponding starting material.

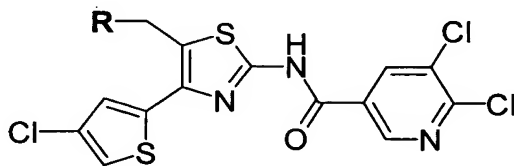
(Table 7)



Rf	X, Y	Data
32	X= N, Y=C-Cl	MS;583.
33	X= C-F, Y= C-F	MS;584.

Compounds in Reference Examples 34 and 35 shown in Table 8 were produced in the same manner as in Example 1 to be described later using the corresponding starting materials respectively.

(Table 8)



Rf	R	Data
34	pipe	MS;487.
35	nBuN(Me)	MS;489.

Reference Example 36

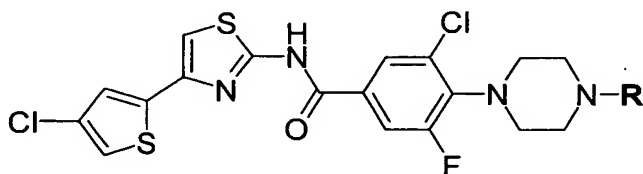
A 4M HCl-EtOAc solution was added to a chloroform-EtOH mixed solution of the compound in Reference Example 19 under ice cooling, and the mixture was stirred at room temperature for 17 hours to obtain 3-chloro-N-[4-(4-chlorothiophen-2-

yl)thiazol-2-yl]-5-fluoro-4-piperazin-1-ylbenzamide
hydrochloride.

Reference Example 37

5 Potassium carbonate and ethyl bromoacetate were added
to a DMF solution of the compound in Reference Example 36,
and the mixture was stirred at room temperature for 23 hours
to obtain ethyl [4-(2-chloro-4-{[4-(4-chlorothiophen-2-
yl)thiazol-2-yl]carbamoyl}-6-fluorophenyl)piperazin-1-
10 yl]acetate.

(Table 9)



Rf	R	Data
36	H	MS;457.
37	EtO ₂ CCH ₂	MS;543.

15 Reference Example 38

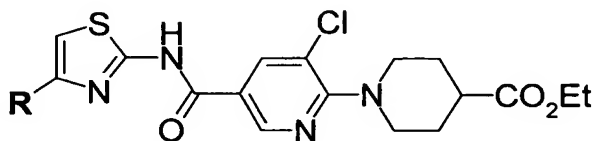
Phosphorus oxychloride was added to a pyridine
suspension of 2-amino-4-[3-(trifluoromethyl)phenyl]thiazole
and 5,6-dichloronicotinic acid at -30°C. The temperature
was gradually raised, and the mixture was stirred overnight
20 at room temperature. After the solvent was distilled off
under reduced pressure, pyridine and EtOH were added, and

the mixture was stirred at 50°C for 30 minutes.

Triethylamine and ethyl isonipecotatate were added at room temperature, and the solution was stirred at 80°C for 15 hours to obtain ethyl 1-[3-chloro-5-({4-[3-trifluoromethyl)phenyl]thiazol-2-yl}carbamoyl)-2-pyridyl]piperidine-4-carboxylate.

Compounds in Reference Examples 39 and 40 shown in Table 10 were produced in the same manner as in Reference Example 38 using the corresponding starting materials respectively.

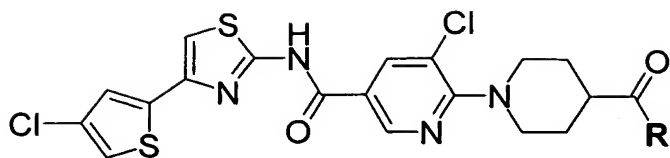
(Table 10)



Rf	R	Data
38	3-F ₃ C-Ph	MS;539.
39	4-F-Ph	MS;489.
40	4-Me-2-The	MS;491.

The compound in Reference Example 41 shown in Table 11 was produced in the same manner as in Reference Example 8, and the compound in Reference Example 42 in the same manner as in Example 8 to be described later, using the corresponding starting materials respectively.

(Table 11)



Rf	R	Data
41	HO	MS;483.
42	MeO ₂ CCH ₂ NH	MS;554.

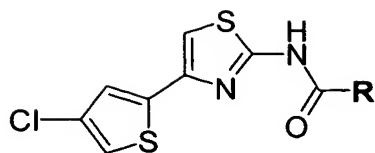
Reference Example 43

Phenyl chloroformate and pyridine were added to a THF solution of the compound in Reference Example 13, and the mixture was stirred at room temperature for 1.5 hours to obtain phenyl N-[4-(4-chlorothiophen-2-yl)thiazol-2-yl]carbamate.

Reference Example 44

A mixture of ethyl N-(piperidin-4-yl)isonipecotate hydrochloride and isopropyl N-(piperidin-4-yl)isonipecotate and triethylamine were added to a DMF solution of the compound in Reference Example 43, and the mixture was stirred at 80°C for 12 hours to obtain an ester mixture. The ester mixture was dissolved in MeOH, and triethylamine and sodium ethoxide were added. The solution was stirred at from room temperature to 50°C for 18 hours to obtain methyl 1'-{[4-(4-chlorothiophen-2-yl)thiazol-2-yl]carbamoyle}-1,4'-bipiperidine-4-carboxylate.

(Table 12)



Rf	R	Data
43	PhO	MS;337.
44	4-(4-MeO ₂ C-pipe)pipe	MS;469.

Reference Example 45

The compound in Reference Example 45 shown in Table 13 was produced in the same manner as in Reference Example 13 using 4-(4-chlorothiophen-2-yl)-4-oxobutanoic acid ester (methyl ester:ethyl ester 3:2 mixture) as a starting material.

Reference Example 46

A compound in Reference Example 46 shown in Table 13 was produced in the same manner as in Reference Example 8 using the corresponding starting material.

Reference Example 47

Butylmethylaniline, WSC-HCl, HOBT and triethylamine were added to a DMF solution of the compound in Reference Example 46, and the mixture was stirred at room temperature for 18 hours to obtain N-butyl-N-methyl-[2-amino-4-(4-chlorothiophen-2-yl)thiazol-5-yl]acetamide.

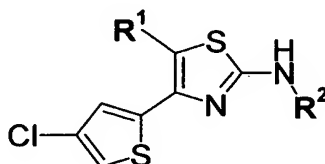
Reference Example 48

A THF solution of the compound in Reference Example 47 was added to a THF suspension of lithium aluminum hydride, and the mixture was stirred under reflux for 3 hours to obtain 2-amino-5-{2-[butyl(methyl)amino]ethyl}-4-(4-chlorothiophen-2-yl)thiazole.

Reference Example 49

A compound in Reference Example 49 shown in Table 13 was produced in the same manner as in Reference Example 15 using the corresponding starting material.

(Table 13)



Rf	R ¹ , R ²	Data
45	R ¹ = RO ₂ CCH ₂ (R; Me:Et=3:2), R ² = H	GC-MS;288,302.
46	R ¹ = HO ₂ CCH ₂ , R ² = H	MS;275.
47	R ¹ = nBuN(Me)COCH ₂ , R ² = H	MS;344.
48	R ¹ = nBuN(Me)(CH ₂) ₂ , R ² = H	MS;330.
49	R ¹ = nBuN(Me)(CH ₂) ₂ , R ² = 5,6-diCl-3-Py-CO-	MN;501,503.

15

Reference Example 50

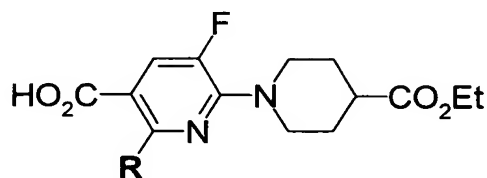
Ethyl isonipecotate was added to a DMF solution of 2,6-dichloro-5-fluoronicotinic acid, and the mixture was

stirred at 80°C to obtain 2-chloro-6-[4-(ethoxycarbonyl)piperidin-1-yl]-5-fluoronicotinic acid.

Reference Example 51

Triethylamine and 10% palladium supported on carbon were added to a THF-EtOH solution of the compound in Reference Example 50, and the mixture was stirred at room temperature in a 4-atm hydrogen atmosphere to obtain 6-[4-(ethoxycarbonyl)piperidin-1-yl]-5-fluoronicotinic acid.

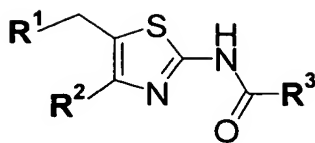
(Table 14)



Rf	R	Data
50	Cl	MS; 331.
51	H	MS; 297.

Compounds in Reference Examples 52 and 53 shown in Table 15 were produced in the same manner as in Example 3 to be described later, compounds in Reference Examples 54 to 56 shown in Table 15 in the same manner as in Reference Example 15 and compounds in Reference Examples 57 to 64 shown in Table 15 in the same manner as in Example 1 to be described later, using the corresponding starting materials respectively.

(Table 15)



Rf	R ¹	R ²	R ³	Data
52	H	4-Cl-2-The	5-Cl-6-(MeO ₂ C(CH ₂) ₂ N(Me))-3-Py	MN; 471.
53	H	4-Cl-2-The	5-Cl-6-(MeO ₂ C(CH ₂) ₃ N(Me))-3-Py	MN; 483.
54	H	4-Cl-2-The	5-F-6-(4-EtO ₂ C-pipe)-3-Py	MS; 495.
55	H	4-Cl-2-The	3-F ₃ C-4-Me-Ph	MS; 403.
56	H	4-Me-2-The	5,6-diCl-3-Py	MS; 370.
57	iPrN(Me)-	4-Cl-2-The	5,6-diCl-3-Py	MS; 475,477.
58	iBuN(Me)-	4-Cl-2-The	5,6-diCl-3-Py	MS; 491.
59	2-Me-pyrr-	4-Cl-2-The	5,6-diCl-3-Py	MS; 487.
60	(S)-2-Me-pyrr-	4-Cl-2-The	5,6-diCl-3-Py	MS; 487.
61	(R)-2-Me-pyrr-	4-Cl-2-The	5,6-diCl-3-Py	MS; 487.
62	iBuN(Me)-	4-Me-2-The	5,6-diCl-3-Py	MS; 469.
63	cBuCH ₂ N(Me)-	4-Me-2-The	5,6-diCl-3-Py	MS; 481.
64	2-Me-pyrr-	4-Me-2-The	5,6-diCl-3-Py	MS; 467.

Example 1

5 3 ml of acetic acid, 24 μ l of a formaldehyde aqueous
 solution (36%) and 47 μ l of N-butyl-N-methylamine were added
 to 150 mg of ethyl 1-(3-chloro-5-{[4-(4-chlorothiophen-2-
 yl)thiazol-2-yl]carbamoyl}-2-pyridyl)piperidine-4-
 carboxylate, and the mixture was stirred at 90°C for 18
 10 hours. After the solvent was distilled off under reduced
 pressure, a saturated sodium hydrogencarbonate aqueous
 solution was added. The mixture was extracted with
 chloroform, and dried over magnesium sulfate. The solvent
 was distilled off under reduced pressure, and the resulting
 15 residue was purified by silica gel column chromatography

using hexane:EtOAc (7:1 to 5:1) as an elution solvent to obtain 147 mg of ethyl 1-(5-{[5-{[butyl(methyl)amino]methyl}-4-(4-chlorothiophen-2-yl)thiazol-2-yl]carbamoyl}-3-chloro-2-pyridyl)piperidine-4-carboxylate.

Example 2

39 μ l of N-(2-methoxyethyl)methylamine, 51 μ l of triethylamine and 23 mg of 4-(dimethylamino)pyridine were added to a 6 ml EtOH suspension of 107 mg of ethyl 1-(5-{[5-{[acetoxymethyl]-4-(4-chlorothiophen-2-yl)thiazol-2-yl]carbamoyl}-3-chloro-2-pyridyl)piperidine-4-carboxylate, and the mixture was stirred at 50°C for 2 hours. After the solvent was distilled off, a saturated sodium hydrogencarbonate aqueous solution was added, and the mixture was extracted with EtOAc, and washed with water and with brine(saturated sodium chloride aqueous solution). The resulting product was dried over magnesium sulfate, and the solvent was then distilled off under reduced pressure. The resulting residue was purified by silica gel column chromatography using a hexane:EtOAc (10:1 to 3.5:1) as an elution solvent to obtain 90 mg of ethyl 1-{3-chloro-5-[(4-(4-chlorothiophen-2-yl)-5-{[(2-methoxyethyl)(methyl)amino]methyl}thiazol-2-yl)carbamoyl]-2-pyridyl)piperidine-4-carboxylate.

Example 3

110 μ l of a formaldehyde aqueous solution (35%) and 76 μ l of acetic acid were added to 2 ml of 1,2-dichloroethane solution of 79 mg of ethyl 1-[3-chloro-5-({4-(4-chlorothiophen-2-yl)-5-[(cyclobutylamino)methyl]thiazol-2-yl}carbamoyl)-2-pyridyl]piperidine-4-carboxylate, and the mixture was stirred at room temperature for 1 hour. Subsequently, 45 mg of $\text{NaBH}(\text{OAc})_3$ was added, and the solution was stirred at room temperature for 1 hour.

10 Chloroform was added to the reaction solution, and the organic layer was washed with a saturated sodium hydrogencarbonate aqueous solution, with water and with brine, and then dried over sodium sulfate. After the solvent was distilled off, the residue was purified by

15 silica gel column chromatography (hexane:EtOAc = 4:1 to 2:1) to obtain 58mg of ethyl 1-{3-chloro-5-[(4-(4-chlorothiophen-2-yl)-5-{[cyclobutyl(methyl)amino]methyl}thiazol-2-yl)carbamoyl]-2-pyridyl}piperidine-4-carboxylate.

20

Example 4

1.3 ml of ethyl isonipecotate was added to a 5 ml THF solution of 413 mg of 5,6-dichloro-N-[4-(4-chlorothiophen-2-yl)-5-(piperidin-1-ylmethyl)-1,3-thiazol-2-yl]nicotinamide, and the mixture was stirred for 5 days. After the solvent

25 was distilled off under reduced pressure, a saturated sodium hydrogencarbonate aqueous solution was added, and the

resulting precipitate was collected by filtration. The precipitate was dissolved in chloroform, and a saturated sodium hydrogencarbonate aqueous solution was added. The mixture was extracted with chloroform, and dried over magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified by silica gel column chromatography using hexane:EtOAc (4:1 to 3:1) as an elution solvent to obtain 468 mg of ethyl 1-(3-chloro-5-([4-(4-chlorothiophen-2-yl)-5-(piperidinomethyl)thiazol-2-yl]carbamoyl)-2-pyridyl)piperidine-4-carboxylate.

Example 5

0.4 ml of a 1M sodium hydroxide aqueous solution was added to a 1.5 ml EtOH suspension of 76 mg of ethyl 1-(3-chloro-5-([4-(4-chlorothiophen-2-yl)-5-((2-methoxyethyl)(methyl)amino)methyl)thiazol-2-yl]carbamoyl)-2-pyridyl)piperidine-4-carboxylate, and the mixture was stirred at 60°C for 2 hours. 0.6 ml of 1M hydrochloric acid and 0.5 ml of water were added at room temperature, and the resulting precipitate was collected by filtration, washed with 50% ethanol water, and dried under reduced pressure to obtain 73 mg of 1-(3-chloro-5-([4-(4-chlorothiophen-2-yl)-5-((2-methoxyethyl)(methyl)amino)methyl)thiazol-2-yl]carbamoyl)-2-pyridyl)piperidine-4-carboxylic acid hydrochloride.

Example 6

19 mg of sodium boron hydride was added to a 5 ml THF solution of 128mg of ethyl [4-(5-{5-
5 { [butyl(methyl)amino]methyl)-4-(4-chlorothiophen-2-yl)thiazol-2-yl]carbamoyl}-3-chloro-2-pyridyl)-2-oxopiperazin-1-yl]acetate, and the mixture was refluxed with stirring. A solution of 128 mg of MeOH in 2 ml of THF was slowly added thereto dropwise, and the mixture was stirred
10 under reflux for 1 hour. The reaction solution was ice-cooled, and water was then added. The solution was extracted with chloroform, washed with brine, and then dried over magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified by
15 silica gel column chromatography using chloroform:MeOH (99:1 to 98:2) as an elution solvent. The resulting crude product was suspended in methanol, and insoluble matters were removed by filtration. Then, the solvent was distilled off under reduced pressure. The thus-obtained residue was
20 dissolved in EtOAc, and a 4M HCl-EtOAc solution was added, followed by stirring. The resulting precipitate was then collected by filtration, and dried under reduced pressure to obtain 15 mg of N-[5-{[butyl(methyl)amino]methyl)-4-(4-chlorothiophen-2-yl)thiazol-2-yl]-5-chloro-6-[4-(2-
25 hydroxyethyl)-3-oxopiperazin-1-yl]nicotinamide hydrochloride.

Example 7

40 mg of the compound in Example 132 was dissolved in 6 ml of MeOH, and 1.6 ml of conc. hydrochloric acid was added, followed by stirring for 2 hours. Then, concentration was conducted, and the precipitate was filtered, and washed with EtOAc to obtain 32 mg of N-[5-{[butyl(methyl)amino]methyl}-4-(4-chlorothiophen-2-yl)thiazol-2-yl]-4-(2-hydroxymethoxy)-3-methoxybenzamide hydrochloride.

Example 8

30 μ l of triethylamine, 30 μ l of morpholine, 45 mg of WSC·HCl and 30 mg of HOBt were added to 2 ml of a THF solution of 52 mg of 1-{3-chloro-5-[(4-(4-chlorothiophen-2-yl)-5-[(3-methoxypropyl)(methyl)amino]methyl)thiazol-2-yl)carbamoyl]-2-pyridyl}piperidine-4-carboxylic acid hydrochloride, and the mixture was stirred overnight at room temperature. Chloroform was added to the reaction solution. The organic layer was washed with a saturated sodium hydrogencarbonate aqueous solution, with water and with brine, and then dried over sodium sulfate. After the solvent was distilled off, the residue was purified by silica gel column chromatography (eluent: chloroform:MeOH = 100:1 to 50:1, hexane:EtOAc = 2:1, then chloroform:MeOH = 20:1), and suspended in 2 ml of diethyl ether. 2 ml of 4N

HCl-EtOAc was added, and the precipitate was collected by filtration to obtain 25 mg of 5-chloro-N-(4-(4-chlorothiophen-2-yl)-5-[[3-methoxypropyl)(methyl)amino]methyl}thiazol-2-yl)-6-[4-(morpholinocarbonyl)piperidino]nicotinamide hydrochloride.

Example 9

3 ml of a 4M HCl-dioxane solution was added to 188 mg of the compound in Example 190, and the mixture was stirred at 50°C for 18 hours. The reaction solution was cooled at room temperature, and the solid precipitated was then filtered to obtain 160 mg of [(1-{3-chloro-5-[(4-(4-chlorothiophen-2-yl)-5-[[2-methoxyethyl)(methyl)amino]methyl}thiazol-2-yl)carbamoyl]-2-pyridyl)-4-piperidyl]oxy]acetic acid hydrochloride.

Example 10

200 mg of the compound in Reference Example 23 was dissolved in 5 ml of formic acid, and 37 µl of methoxyethylamine and 92 µl of a formaldehyde aqueous solution (35%) were added, followed by stirring at 70°C for 15 hours. After the reaction solution was concentrated, chloroform was added, and the organic layer was washed with a saturated sodium hydrogencarbonate aqueous solution, with water and with brine, followed by drying over sodium sulfate. After the solvent was distilled off, the residue

was purified by silica gel column chromatography
(hexane:EtOAc = 5:1 to 3:1) to obtain 110 mg of ethyl 1-(3-
chloro-5-([7-chloro-5-(2-methoxyethyl)-5,6-dihydro-4H-
thiazolo[5,4-c]thieno[2,3-e]azepin-2-yl]carbamoyl)-2-
5 pyridine)-4-carboxylate.

Example 11

100 mg of 6-[(2-aminoethyl)amino]-N-[5-
{[butyl(methyl)amino]methyl}-4-(4-chlorothiophen-2-
10 yl)thiazol-2-yl]-5-chloronicotinamide trihydrochloride was
suspended in 5 ml of THF, and 85 μ l of triethylamine was
added, followed by cooling to 0°C. 13 μ l of methanesulfonyl
chloride was added to the solution, and the mixture was
stirred at room temperature for 2 hours. The reaction
15 solution was poured into water, and extracted with
chloroform. The organic layer was washed with water and
with brine, and then dried over magnesium sulfate. After
the solvent was distilled off, the residue was purified by
silica gel column chromatography (chloroform:MeOH = 10:1) to
20 obtain 75 mg of N-[5-{[butyl(methyl)amino]methyl}-4-(4-
chlorothiophen-2-yl)thiazol-2-yl]-5-chloro-6-({2-
[(methanesulfonyl)amino]ethyl}amino)nicotinamide.

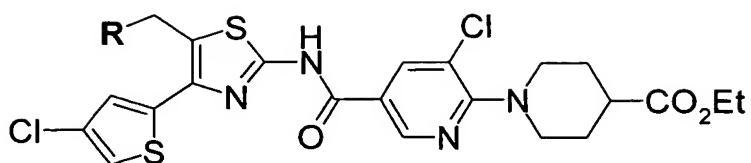
The structures and the physical data of the compounds
in Examples are shown in Tables 16 to 26 below. Symbols in
25 the tables have the following meanings (this applies to the
following).

Ex: Example No. (When only a numeral is shown in column Ex., it is indicated that the compound in this Example No. is a free compound, and when a slash "/" and "HCl" are described next to a numeral, it is indicated that
5 the compound in this Example No. was hydrochloride.)

Syn: Process (A numeral indicates that a compound was synthesized in the same manner as the compound in Example to which the numeral is allotted as Example No., using the corresponding starting material.)

10 R: Substituent in the general formula (nPr: normal propyl, cBu: cyclobutyl, cHex: cyclohexyl, MOM: methoxymethyl, Ac: acetyl, Ms: methanesulfonyl, THF: tetrahydrofuryl, THP: tetrahydropyranyl)

(Table 16)

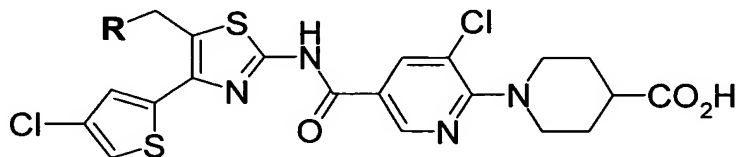


Ex	Syn	R	Data
1	1	nBuN(Me)-	MS; 610.
2	2	MeO(CH ₂) ₂ N(Me)-	MS; 612.
3	3	cBuN(Me)-	MS; 608.
4	4	pipe-	MS; 608.
12	1	Me ₂ N-	MS; 568.
13	1	pyrr-	MS; 594.
14	1	mor-	MS; 610.
15	1	4-Me-pipa-	MS; 623.
16	1	4-cHex-pipa-	MS; 691.
17	1	Et ₂ N-	MS; 650.
18	1	EtO(CH ₂) ₂ N(Me)-	MS; 626.
19	1	(2-THF)CH ₂ N(Me)-	MS; 638.
20	1	nPrO(CH ₂) ₂ N(Me)-	MS; 640.
21	1	EtO(CH ₂) ₂ N(Et)-	MS; 640.
22	1	iPrO(CH ₂) ₂ N(Me)-	MS; 640.
23	1	4-(3-F-pyrr)pipe-	MS; 694.
24	1	MeO(CH ₂) ₃ N(Me)-	MS; 625.
25	1	MeO(CH ₂) ₂ N(Et)-	MS; 626.
26	1	(2S,6R)-2,6-diMe-mor-	MS; 638.
27	1	4-EtO ₂ C-pipe-	MN; 678.
28	1	iPrN(Me)-	MS; 596.
29	1	2-Me-pyrr-	MS; 608.
30	1	(S)-2-Me-pyrr-	MS; 608.
31	1	(R)-2-Me-pyrr-	MS; 608.
32	1	(R)-3-Me-pyrr-	MS; 608.
33	1	(S)-3-Me-pyrr-	MS; 608.
34	1	3-EtO-pyrr-	MS; 638.
35	1	4-MeO-pipe-	MS; 638.
36	1	3-MeO-pipe-	MS; 638.
37	1	(S)-2-MeOCH ₂ -pyrr-	MS; 638.
38	1	(R)-2-MeOCH ₂ -pyrr-	MS; 638.
39	2	(R)-MeOCH ₂ CH(Me)N(Me)	MS; 626.
40	2	(S)-MeOCH ₂ CH(Me)N(Me)	MS; 626.
41	2	azet-	MS; 580.
42	2	Azepan-1-yl	MS; 622.
43	2	Azocan-1-yl	MS; 636.
44	2	Azonan-1-yl	MS; 650.

(Table 16 Continued)

Ex	Syn	R	Data
45	2	Azecan-1-yl	MS; 664.
46	2	(2R,6S)-2,6-diMe-pipe	MS; 636.
47	2	Me ₂ N(CH ₂) ₂ N(Me)-	MS; 625.
48	2	cHexN(Me)-	MS; 636.
49	2	MeO(CH ₂) ₂ NH-	MS; 597.
50	2	cPrNH-	MS; 580.
51	2	cBuNH-	MS; 594.
52	2	cHexNH-	MS; 622.
53	2	iPrNH-	MS; 582.
54	2	tBuNH-	MS; 596.
55	2	(4-THP)NH-	MS; 624.
56	2	(3-THF)NH-	MS; 610.
57	2	MeOCH ₂ CH(Me)NH-	MS; 612.
58	3	(4-THP)N(Me)-	MS; 638.
59	3	(3-THF)N(Me)-	MS; 624.
60	3	MeOCH ₂ CH(Me)N(Me)-	MS; 626.
61	3	cPrN(Me)-	MS; 594.
62	3	iBuN(Me)-	MS; 610.
63	10	(R)-(MeO)(Me)CHCH ₂ N(Me)-	MS; 626.
64	10	(S)-(MeO)(Me)CHCH ₂ N(Me)-	MS; 626.

(Table 17)

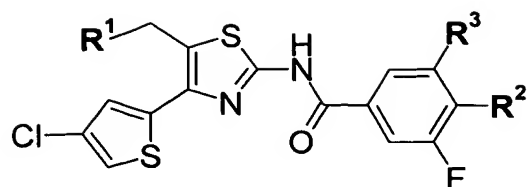


Ex	Syn	R	Data
5/HCl	5	MeO(CH ₂) ₂ N(Me)-	MS; 584.
65/HCl	5	Me ₂ N-	MS; 540.
66/HCl	5	pyrr-	MS; 566.
67/HCl	5	mor-	MN; 580.
68/HCl	5	4-Me-pipa-	MS; 595.
69/HCl	5	4-cHex-pipa-	MS; 663.
70/HCl	5	Et ₂ N-	MS; 568.
71/HCl	5	nBuN(Me)-	MS; 582.
72/HCl	5	EtO(CH ₂) ₂ N(Me)-	MS; 598.
73/HCl	5	(2-THF)CH ₂ N(Me)-	MS; 610.
74/HCl	5	nPrO(CH ₂) ₂ N(Me)-	MS; 612.
75/HCl	5	EtO(CH ₂) ₂ N(Et)-	MS; 612.
76/HCl	5	iPrO(CH ₂) ₂ N(Me)-	MS; 612.
77/HCl	5	4-(3-F-pyrr)pipe-	MS; 667.

(Table 17 Continued)

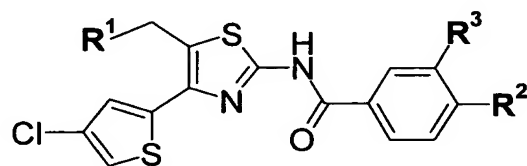
Ex	Syn	R	Data
78/HCl	5	MeO(CH ₂) ₃ N(Me)-	MN; 596.
79/HCl	5	MeO(CH ₂) ₂ N(Et)-	MS; 598.
80	5	(2S,6R)-2,6-diMe-mor-	MN; 608.
81/HCl	5	(R)-MeOCH ₂ CH(Me)N(Me)-	MS; 598.
82/HCl	5	(S)-MeOCH ₂ CH(Me)N(Me)-	MS; 598.
83/HCl	5	azet-	MS; 552.
84/HCl	5	Azepan-1-yl	MS; 594.
85/HCl	5	Azocan-1-yl	MS; 608.
86/HCl	5	Azonan-1-yl	MS; 622.
87/HCl	5	Azecan-1-yl	MS; 636.
88/HCl	5	(2R,6S)-2,6-diMe-pipe-	MS; 608.
89/HCl	5	Me ₂ N(CH ₂) ₂ N(Me)-	MS; 597.
90/HCl	5	cHexN(Me)-	MS; 608.
91/HCl	5	MeO(CH ₂) ₂ NH-	MS; 569.
92/HCl	5	cPrNH-	MN; 550.
93/HCl	5	cBuNH-	MN; 564.
94/HCl	5	cHex-NH-	MN; 592.
95/HCl	5	iPrNH-	MN; 552.
96/HCl	5	tBuNH-	MN; 566.
97/HCl	5	(4-THP)N(Me)-	MS; 610.
98/HCl	5	(3-THF)N(Me)-	MS; 596.
99/HCl	5	MeOCH ₂ CH(Me)N(Me)-	MS; 598.
100/HCl	5	cBuN(Me)-	MS; 580.
101/HCl	5	cPrN(Me)-	MS; 566.
102/HCl	5	pipe-	MN; 578.
103/HCl	5	iBuN(Me)-	MS; 582.
104/HCl	5	iPrN(Me)-	MS; 568.
105/HCl	5	2-Me-pyrr-	MS; 580.
106/HCl	5	(S)-2-Me-pyrr-	MS; 580.
107/HCl	5	(R)-2-Me-pyrr-	MS; 580.
108/HCl	5	(R)-3-Me-pyrr-	MS; 580.
109/HCl	5	(S)-3-Me-pyrr-	MS; 580.
110/HCl	5	(R)-MeOCH(Me)CH ₂ N(Me)-	MS; 598.
111/HCl	5	(S)-MeOCH(Me)CH ₂ N(Me)-	MS; 598.
112/HCl	5	3-EtO-pyrr-	MS; 610.
113/HCl	5	4-MeO-pipe-	MS; 610.
114/HCl	5	3-MeO-pipe-	MS; 610.
115/HCl	5	(S)-2-MeOCH ₂ -pyrr-	MS; 610.
116/HCl	5	(R)-2-MeOCH ₂ -pyrr-	MS; 610.

(Table 18)



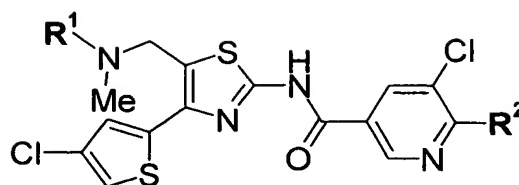
Ex	Syn	R ¹	R ²	R ³	Data
117	1	MeO(CH ₂) ₂ N(Me)-	4-(EtO ₂ CCH ₂)pipa-	Cl	MS; 644.
118	1	nBuN(Me)-	4-(EtO ₂ CCH ₂)pipa-	Cl	MS; 642.
119/HCl	1	nBuN(Me)-	HO(CH ₂) ₃ O-	Cl	MS; 546.
120/HCl	1	nBuN(Me)-	AcO(CH ₂) ₃ O-	Cl	MS; 588.
121	1	iBuN(Me)-	MeO ₂ C(CH ₂) ₃ O-	H	MM: 554.
122	2	Azocan-1-yl	4-EtO ₂ C-pipe	F	MS; 637.
123	2	nBuN(Me)-	4-EtO ₂ C-pipe	F	MS; 611.
124/HCl	5	MeO(CH ₂) ₂ N(Me)-	4-(HO ₂ CCH ₂)pipa-	Cl	MN; 614.
125/HCl	5	nBuN(Me)-	4-(HO ₂ CCH ₂)pipa-	Cl	MS; 614.
126/HCl	5	Azocan-1-yl	4-HO ₂ C-pipe	F	MS; 609.
127/HCl	5	nBuN(Me)-	4-HO ₂ C-pipe	F	MS; 583.
128/HCl	5	iBuN(Me)-	HO ₂ C(CH ₂) ₃ O-	H	MN; 538.

(Table 19)



Ex	Syn	R ¹	R ²	R ³	Data
7/HCl	7	nBuN(Me)-	HO(CH ₂) ₂ O-	OMe	MS; 510
129	1	nBuN(Me)-	OMOM	Cl	MS; 514.
130/HCl	1	nBuN(Me)-	OH	Cl	MS; 470.
131	1	nBuN(Me)-	MeO ₂ C(CH ₂) ₃ O-	F	MS; 554.
132	1	nBuN(Me)-	TBSO(CH ₂) ₂ O-	OMe	MS; 624.
133	1	nBuN(Me)-	Me	CF ₃	MS; 502.
134/HCl	5	nBuN(Me)-	HO ₂ C(CH ₂) ₃ O-	F	MS; 540.

(Table 20)

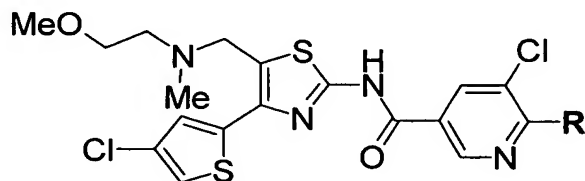


Ex	Syn	R ¹	R ²	Data
6/HCl	6	nBu	3-oxo-4-HO(CH ₂) ₂ -pipa-	MS; 597.
11/HCl	11	nBu	MsHN(CH ₂) ₂ NH-	MS; 591.
135	1	nBu	3-MeO ₂ C-pyrr-	MS; 582.
136	1	nBu	(R)-3-(MeO ₂ CCH ₂ O)pyrr-	MS; 612.
137	1	nBu	(S)-3-MeO ₂ C-pyrr-	MS; 582.
138	1	nBu	3-EtO ₂ C-azet-	MS; 582.
139	1	nBu	4-(tBuO ₂ CCH ₂ O)pipe-	MS; 668.
140	1	nBu	2-EtO ₂ C-mor-	MS; 612.
141	1	nBu	4-(MeO ₂ CCH ₂ NHCO)pipe-	MS; 653.
142	3	nBu	4-OH-4-EtO ₂ C-pipe-	MS; 626.
143	3	nBu	tBuO ₂ C(CH ₂) ₂ NH-	MS; 598.
144	3	iBu	3-(EtO ₂ CCH ₂)azet-	MS; 596.
145	3	iBu	EtO ₂ C(CH ₂) ₃ NH-	MS; 584.
146	3	iBu	tBuO ₂ C(CH ₂) ₂ NH-	MS; 598.
147	3	iBu	MeO ₂ C(CH ₂) ₃ N(Me)-	MS; 584.
148	3	iBu	EtO ₂ C(CH ₂) ₂ N(Me)-	MS; 584.
149	3	iBu	EtO ₂ CCH ₂ N(Me)-	MS; 570.
150/HCl	4	nBu	4-HOCH ₂ -pipe-	MS; 568.
151/HCl	4	nBu	HO(CH ₂) ₃ NH-	MS; 528.
152/HCl	4	nBu	MeO(CH ₂) ₂ O(CH ₂) ₂ NH-	MS; 572.
153/HCl	4	nBu	3-oxo-pipa-	MS; 553.
154/HCl	4	nBu	H ₂ N(CH ₂) ₂ NH-	MS; 513.
155	4	nBu	4-(4-MeO ₂ C-pipe)-pipe-	MS; 679.
156	4	nBu	3-oxo-4-EtO ₂ CCH ₂ -pipa-	MS; 639.
157	4	nBu	EtO ₂ C(CH ₂) ₃ NH-	MS; 584.
158/HCl	5	nBu	HO ₂ C(CH ₂) ₃ NH-	MS; 556.
159/HCl	5	nBu	4-(4-HO ₂ C-pipe)-pipe-	MN; 663.
160/HCl	5	nBu	3-oxo-4-HO ₂ CCH ₂ -pipa-	MS; 611.
161/HCl	5	nBu	3-HO ₂ C-pyrr-	MS; 568.
162/HCl	5	nBu	(R)-3-(HO ₂ CCH ₂ O)-pyrr-	MN; 596.
163/HCl	5	nBu	(S)-3-HO ₂ C-pyrr-	MS; 568.
164/HCl	5	nBu	3-HO ₂ C-azet-	MS; 554.
165/HCl	5	nBu	2-HO ₂ C-mor-	MS; 584.
166/HCl	5	nBu	4-(3-HO ₂ C-azet-CO)pipe-	MN; 663.
167/HCl	5	nBu	4-(HO ₂ C(CH ₂) ₂ NHCO)pipe-	MS; 653.

(Table 20 Continued)

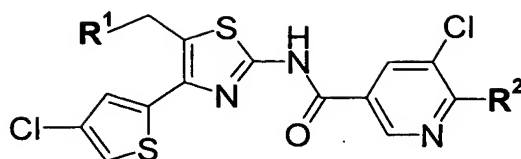
Ex	Syn	R ¹	R ²	Data
168/HCl	5	nBu	4-(HO ₂ CCH ₂ NHCO)pipe-	MS; 639.
169/HCl	5	nBu	4-HO-4-HO ₂ C-pipe-	MS; 598.
170/HCl	5	iBu	3-(HO ₂ CCH ₂)azet-	MS; 568.
171/HCl	5	iBu	HO ₂ C(CH ₂) ₃ NH-	MS; 556.
172/HCl	5	iBu	HO ₂ C(CH ₂) ₃ N(Me)-	MS; 570.
173/HCl	5	iBu	HO ₂ C(CH ₂) ₂ N(Me)-	MS; 556.
174/HCl	5	iBu	HO ₂ CCH ₂ N(Me)-	MS; 542.
175	8	nBu	4-(3-EtO ₂ C-azet-CO)pipe	MS; 693.
176/HCl	8	nBu	4-(MeO(CH ₂) ₂ NHCO)pipe	MS; 639.
177/HCl	8	nBu	4-(H ₂ NCOCH ₂ NHCO)pipe	MS; 638.
178/HCl	8	nBu	4-(MeO(CH ₂) ₂ O(CH ₂) ₂ NHCO)pipe-	MS; 683.
179	8	nBu	4-(EtO ₂ C(CH ₂) ₂ NHCO)pipe-	MS; 681.
180	8	nBu	4-(HO(CH ₂) ₂ NHCO)pipe-	MS; 625.
181/HCl	9	nBu	4-HO ₂ CCH ₂ O-pipe-	MS; 612.
182/HCl	9	nBu	HO ₂ C(CH ₂) ₂ NH-	MS; 542.
183/HCl	9	iBu	HO ₂ C(CH ₂) ₂ NH-	MS; 542.

(Table 21)



Ex	Syn	R	Data
9/HCl	9	4-(HO ₂ CCH ₂ O)pipe-	MN; 612.
184	1	3-EtO ₂ C-pipe-	MS; 612.
185	1	3-MeO ₂ C-pyrr-	MS; 584.
186	1	(R)-3-(MeO ₂ CCH ₂ O)pyrr-	MS; 614.
187	1	4-EtO ₂ CCH ₂ -pipe-	MS; 626.
188	1	2-EtO ₂ C-mor-	MN; 612.
189	1	3-EtO ₂ C-azet-	MS; 584.
190	1	4-(tBuO ₂ CCH ₂ O)-pipe-	MS; 670.
191/HCl	5	3-HO ₂ C-pipe-	MS; 584.
192/HCl	5	3-HO ₂ C-pyrr	MS; 570.
193/HCl	5	(R)-3-(HO ₂ CCH ₂ O)pyrr-	MS; 600.
194/HCl	5	4-HO ₂ CCH ₂ -pipe-	MS; 598.
195/HCl	5	2-HO ₂ C-mor-	MS; 586.
196/HCl	5	3-HO ₂ C-azet-	MS; 556.

(Table 22)

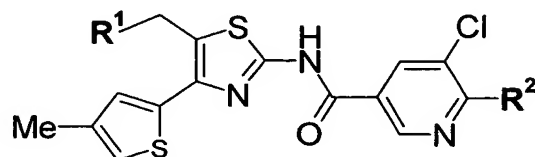


Ex	Syn	R ¹	R ²	Data
8/HCl	8	MeO(CH ₂) ₃ N(Me)-	4-(mor-CO)pipe-	MS; 667.
197	8	MeO(CH ₂) ₃ N(Me)-	4-(MeO(CH ₂) ₂ NHCO)pipe-	MS; 655.
198	1	Me ₂ N-	3-MeO ₂ C-pyrr-	MN; 538.
199	1	(S)-2-Me-pyrr-	MeO ₂ C(CH ₂) ₃ N(Me)-	MS; 582.
200	1	(R)-2-Me-pyrr-	MeO ₂ C(CH ₂) ₃ N(Me)-	MS; 582.
201	1	Et ₂ CHN(Me)-	MeO ₂ C(CH ₂) ₃ N(Me)-	MS; 598.
202	1	(S)-3-Me-pyrr-	MeO ₂ C(CH ₂) ₃ N(Me)-	MS; 582.
203	1	2-Me-pyrr-	MeO ₂ C(CH ₂) ₂ N(Me)-	MS; 568.
204	1	iPrN(Me)-	MeO ₂ C(CH ₂) ₂ N(Me)-	MS; 556.
205	1	(nPr)(Me)CHN(Me)-	MeO ₂ C(CH ₂) ₂ N(Me)-	MS; 584.
206	1	(S)-3-Me-pyrr-	MeO ₂ C(CH ₂) ₂ N(Me)-	MS; 568.
207	1	iPrN(Me)-	(S)-MeO ₂ C-pyrr-	MS; 568.
208	3	2-Me-pyrr-	3-(EtO ₂ CCH ₂)azet-	MS; 594.
209	3	(S)-2-Me-pyrr-	3-(EtO ₂ CCH ₂)azet-	MS; 594.
210	3	(R)-2-Me-pyrr-	3-(EtO ₂ CCH ₂)azet-	MS; 594.
211	3	iPrN(Me)-	3-(EtO ₂ CCH ₂)azet-	MS; 582.
212	3	2-Me-pyrr-	MeO ₂ C(CH ₂) ₃ N(Me)-	MS; 582.
213	3	iPrN(Me)-	MeO ₂ C(CH ₂) ₃ N(Me)-	MS; 570.
214	3	2-Me-pyrr-	EtO ₂ C(CH ₂) ₃ NH-	MS; 582.
215	3	(S)-2-Me-pyrr-	EtO ₂ C(CH ₂) ₃ NH-	MS; 582.
216	3	(R)-2-Me-pyrr-	EtO ₂ C(CH ₂) ₃ NH-	MS; 582.
217	3	2-Me-pyrr-	tBuO ₂ C(CH ₂) ₂ NH-	MS; 596.
218/HCl	4	pipe-	4-H ₂ NOC-pipe-	MN; 579.
219/HCl	5	Me ₂ N-	3-HO ₂ C-pyrr-	MS; 526.
220/HCl	5	2-Me-pyrr-	3-(HO ₂ CCH ₂)azet-	MN; 564.
221/HCl	5	(S)-2-Me-pyrr-	3-(HO ₂ CCH ₂)azet-	MN; 564.
222/HCl	5	(R)-2-Me-pyrr-	3-(HO ₂ CCH ₂)azet-	MN; 564.
223/HCl	5	iPrN(Me)-	3-(HO ₂ CCH ₂)azet-	MN; 552.
224/HCl	5	2-Me-pyrr-	HO ₂ C(CH ₂) ₃ N(Me)-	MS; 568.
225/HCl	5	(S)-2-Me-pyrr-	HO ₂ C(CH ₂) ₃ N(Me)-	MS; 568.
226/HCl	5	(R)-2-Me-pyrr-	HO ₂ C(CH ₂) ₃ N(Me)-	MS; 568.
227/HCl	5	iPrN(Me)-	HO ₂ C(CH ₂) ₃ N(Me)-	MS; 556.
228/HCl	5	Et ₂ CHN(Me)-	HO ₂ C(CH ₂) ₃ N(Me)-	MS; 584.
229/HCl	5	(S)-3-Me-pyrr-	HO ₂ C(CH ₂) ₃ N(Me)-	MN; 566.
230/HCl	5	2-Me-pyrr-	HO ₂ C(CH ₂) ₂ N(Me)-	MS; 554.
231/HCl	5	iPrN(Me)-	HO ₂ C(CH ₂) ₂ N(Me)-	MN; 540.

(Table 22 Continued)

Ex	Syn	R ¹	R ²	Data
232/HCl	5	(nPr)(Me)CHN(Me)-	HO ₂ C(CH ₂) ₂ N(Me)-	MS; 570.
233/HCl	5	(S)-3-Me-pyrr-	HO ₂ C(CH ₂) ₂ N(Me)-	MS; 554.
234/HCl	5	2-Me-pyrr-	HO ₂ C(CH ₂) ₃ NH-	MS; 554.
235/HCl	5	(S)-2-Me-pyrr-	HO ₂ C(CH ₂) ₃ NH-	MN; 552.
236/HCl	5	(R)-2-Me-pyrr-	HO ₂ C(CH ₂) ₃ NH-	MN; 552.
237/HCl	5	iPrN(Me)-	(S)-3-HO ₂ C-pyrr-	MN; 552.
238/HCl	9	2-Me-pyrr-	HO ₂ C(CH ₂) ₂ NH-	MN; 538.

(Table 23)

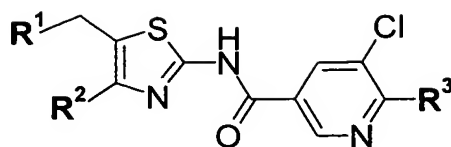


Ex	Syn	R ¹	R ²	Data
239	1	nBuN(Me)-	4-EtO ₂ C-pipe-	MN; 588.
240	1	Me ₂ N-	4-EtO ₂ C-pipe-	MS; 588.
241	1	iBuN(Me)-	4-EtO ₂ C-pipe-	MN; 588.
242	1	cHexN(Me)-	4-EtO ₂ C-pipe-	MS; 588.
243	1	iPrN(Me)-	4-EtO ₂ C-pipe-	MN; 588.
244	1	cBuN(Me)-	4-EtO ₂ C-pipe-	MN; 687.
245	1	Et ₂ CHN(Me)-	4-EtO ₂ C-pipe-	MN; 687.
246	1	(nPr)(Me)CHN(Me)-	4-EtO ₂ C-pipe-	MS; 604.
247	1	(iPr)(Me)CHN(Me)-	4-EtO ₂ C-pipe-	MS; 604.
248	1	tBuN(Me)-	4-EtO ₂ C-pipe-	MS; 590.
249	1	cBuCH ₂ N(Me)-	4-EtO ₂ C-pipe-	MS; 602.
250	1	Azepan-1-yl	4-EtO ₂ C-pipe-	MS; 602.
251	1	4-Me-pipe-	4-EtO ₂ C-pipe-	MS; 602.
252	1	3-Me-pipe-	4-EtO ₂ C-pipe-	MS; 602.
253	1	2-Me-pipe-	4-EtO ₂ C-pipe-	MS; 602.
254	1	2-Me-pyrr-	4-EtO ₂ C-pipe-	MS; 588.
255	1	(S)-2-Me-pyrr-	4-EtO ₂ C-pipe-	MS; 588.
256	1	(R)-2-Me-pyrr-	4-EtO ₂ C-pipe-	MS; 588.
257	1	(R)-3-Me-pyrr-	4-EtO ₂ C-pipe-	MS; 588.
258	1	(S)-3-Me-pyrr-	4-EtO ₂ C-pipe-	MS; 588.
259	1	3,3-diMe-pyrr-	4-EtO ₂ C-pipe-	MN; 600.
260	3	iBuN(Me)-	4-HO-4-EtO ₂ C-pipe-	MS; 606.
261	3	iBuN(Me)-	EtO ₂ C(CH ₂) ₃ NH-	MS; 564.
262	3	iBuN(Me)-	MeO ₂ C(CH ₂) ₃ N(Me)-	MS; 564.
263	3	cBuCH ₂ N(Me)-	4-HO-4-EtO ₂ C-pipe-	ESI-MS(Pos); 618.
264	3	2-Me-pyrr-	4-HO-4-EtO ₂ C-pipe-	MS; 604.

(Table 23 Continued)

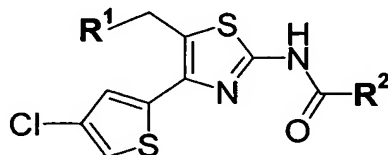
Ex	Syn	R ¹	R ²	Data
265	3	2-Me-pyrr-	EtO ₂ C(CH ₂) ₃ NH-	MS; 562.
266	3	2-Me-pyrr-	MeO ₂ C(CH ₂) ₃ N(Me)-	ESI-MS(Pos); 562.
267/HCl	5	nBuN(Me)-	4-HO ₂ C-pipe-	MS; 562.
268/HCl	5	Me ₂ N-	4-HO ₂ C-pipe-	MS; 520.
269/HCl	5	iBuN(Me)-	4-HO ₂ C-pipe-	MS; 562.
270/HCl	5	cHexN(Me)-	4-HO ₂ C-pipe-	MS; 588.
271/HCl	5	iPrN(Me)-	4-HO ₂ C-pipe-	MS; 548.
272/HCl	5	cBuN(Me)-	4-HO ₂ C-pipe-	MS; 560.
273/HCl	5	Et ₂ CHN(Me)-	4-HO ₂ C-pipe-	MS; 576.
274/HCl	5	(nPr)(Me)CHN(Me)-	4-HO ₂ C-pipe-	MS; 576.
275/HCl	5	(iPr)(Me)CHN(Me)-	4-HO ₂ C-pipe-	MS; 576.
276/HCl	5	cBuCH ₂ N(Me)-	4-HO ₂ C-pipe-	MS; 574.
277/HCl	5	Azepan-1-yl	4-HO ₂ C-pipe-	MS; 574.
278/HCl	5	4-Me-pipe-	4-HO ₂ C-pipe-	MS; 574.
279/HCl	5	3-Me-pipe-	4-HO ₂ C-pipe-	MS; 574.
280/HCl	5	2-Me-pipe-	4-HO ₂ C-pipe-	MS; 574.
281/HCl	5	2-Me-pyrr-	4-HO ₂ C-pipe-	MN; 558.
282/HCl	5	(S)-2-Me-pyrr-	4-HO ₂ C-pipe-	MS; 560.
283/HCl	5	(R)-2-Me-pyrr-	4-HO ₂ C-pipe-	MS; 560.
284/HCl	5	(R)-3-Me-pyrr-	4-HO ₂ C-pipe-	MN; 558.
285/HCl	5	(S)-3-Me-pyrr-	4-HO ₂ C-pipe-	MN; 558.
286/HCl	5	3,3-diMe-pyrr-	4-HO ₂ C-pipe-	MS; 574.
287/HCl	5	iBuN(Me)-	4-HO-4-HO ₂ C-pipe-	MS; 578.
288/HCl	5	iBuN(Me)-	HO ₂ C(CH ₂) ₃ NH-	MS; 536.
289/HCl	5	iBuN(Me)-	HO ₂ C(CH ₂) ₃ N(Me)-	MS; 550.
290/HCl	5	cBuCH ₂ N(Me)-	4-HO-4-HO ₂ C-pipe-	MS; 590.
291/HCl	5	2-Me-pyrr-	4-HO-4-HO ₂ C-pipe-	MS; 576.
292/HCl	5	2-Me-pyrr-	HO ₂ C(CH ₂) ₃ NH-	MS; 534.
293/HCl	5	2-Me-pyrr-	HO ₂ C(CH ₂) ₃ N(Me)-	MS; 548.

(Table 24)



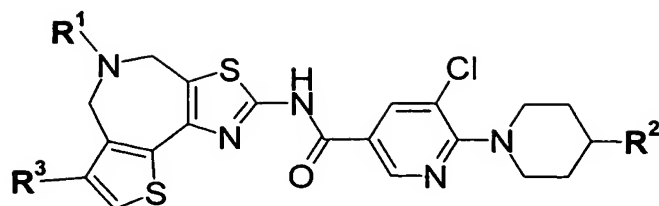
Ex	Syn	R ¹	R ²	R ³	Data
294	1	pipe	4-F-Ph-	4-EtO ₂ C-pipe-	MS; 586.
295	1	pipe	3-F ₃ C-Ph-	4-EtO ₂ C-pipe-	MS; 636.
296	1	nBuN(Me)-	4-F-Ph-	4-EtO ₂ C-pipe-	MS; 588.
297	1	nBuN(Me)-	4-Me-5-(nBuN(Me)CH ₂)-2-The-	4-EtO ₂ C-pipe-	MN; 687.
298/HCl	5	pipe	4-F-Ph-	4-HO ₂ C-pipe-	MS; 558.
299/HCl	5	pipe	3-F ₃ C-Ph-	4-HO ₂ C-pipe-	MS; 608.
300/HCl	5	nBuN(Me)-	4-F-Ph-	4-HO ₂ C-pipe-	MS; 560.

(Table 25)



Ex	Syn	R ¹	R ²	Data
301/HCl	1	pipe	2-MeO-4-Py	MS; 449.
302	1	nBuN(Me)-	4-(4-MeO ₂ C-pipe)pipe	MS; 568.
303	1	nBuN(Me)CH ₂ -	5-Cl-6-(4-EtO ₂ C-pipe)-3-Py	MS; 624.
304	1	nPrN(Me)-	5-F-6-(4-EtO ₂ C-pipe)-3-Py	MS; 580.
305	1	iBuN(Me)-	5-F-6-(4-EtO ₂ C-pipe)-3-Py	MS; 594.
306	1	2-Me-pyrr-	5-F-6-(4-EtO ₂ C-pipe)-3-Py	MS; 592.
307	1	(S)-2-Me-pyrr-	5-F-6-(4-EtO ₂ C-pipe)-3-Py	MS; 592.
308	1	(R)-2-Me-pyrr-	5-F-6-(4-EtO ₂ C-pipe)-3-Py	MS; 592.
309	1	iPrN(Me)-	5-F-6-(4-EtO ₂ C-pipe)-3-Py	MS; 580.
310/HCl	5	nBuN(Me)CH ₂ -	5-Cl-6-(4-HO ₂ C-pipe)-3-Py	MS; 596.
311/HCl	5	nPrN(Me)-	5-F-6-(4-HO ₂ C-pipe)-3-Py	MS; 552.
312/HCl	5	iBuN(Me)-	5-F-6-(4-HO ₂ C-pipe)-3-Py	MS; 566.
313/HCl	5	2-Me-pyrr-	5-F-6-(4-HO ₂ C-pipe)-3-Py	MS; 564.
314/HCl	5	(S)-2-Me-pyrr-	5-F-6-(4-HO ₂ C-pipe)-3-Py	MN; 562.
315/HCl	5	(R)-2-Me-pyrr-	5-F-6-(4-HO ₂ C-pipe)-3-Py	MS; 564.
316/HCl	5	iPrN(Me)-	5-F-6-(4-HO ₂ C-pipe)-3-Py	MN; 550.

(Table 26)



Ex	Syn	R ¹	R ²	R ³	Data
10	10	MeO(CH ₂) ₂ -	EtO ₂ C-	Cl	MS; 610.
317/HCl	5	cBu	HO ₂ C-	Cl	MS; 578.
318/HCl	5	MeO(CH ₂) ₂ -	HO ₂ C-	Cl	MS; 582.
319/HCl	5	(R)-(MeO)(Me)CHCH ₂ -	HO ₂ C-	Cl	MS; 596.
320/HCl	5	(S)-(MeO)(Me)CHCH ₂ -	HO ₂ C-	Cl	MS; 596.
321	5	Me	HO ₂ C-	Cl	ESI-MS(Pos); 538.
322/HCl	5	Me	HO ₂ C-	Me	MS; 518.
323	10	cBu	EtO ₂ C-	Cl	MS; 606.
324	10	(R)-(MeO)(Me)CHCH ₂ -	EtO ₂ C-	Cl	MS; 624.
325	10	(S)-(MeO)(Me)CHCH ₂ -	EtO ₂ C-	Cl	MS; 624.
326	10	Et	EtO ₂ C-	Cl	MN; 578.
327	10	Me	EtO ₂ C-	Cl	ESI-MS(Pos); 566.
328	10	Me	EtO ₂ C-	Me	MS; 546.

NMR data of selected Example compounds are shown in Table 27 below. Each data shows peak δ (ppm) in ¹H-NMR using tetramethylsilane as an internal standard and DMSO- δ_6 as a measuring solvent unless otherwise instructed.

(Table 27)

Ex	Data
5	1.62-1.74(2H,m),1.90-1.98(2H,m),2.52-2.58(1H,m),2.81(3H,s),3.05(2H,t,J=11.2Hz),3.34(5H,s),3.72(2H,brs),4.00(2H,d,J=13.2Hz),4.60-4.90(2H,m),7.65(1H,s),7.73(1H,s),8.43(1H,d,J=1.9Hz),8.87(1H,d,J=2.4Hz),10.33(1H,brs),12.28(1H,brs),13.00(1H,s).
65	1.61-1.73(2H,m),1.90-1.99(2H,m),2.51-2.54(1H,m),2.81(6H,m),3.05(2H,t,J=11.3Hz),4.01(2H,d,J=13.2Hz),4.74(2H,brs),7.69(1H,s),7.72(1H,s),8.43(1H,d,J=1.5Hz),8.87(1H,d,J=1.9Hz),9.95(1H,brs),12.27(1H,brs),12.99(1H,s).
71	0.87(3H,t,J=7.4Hz),1.18-1.32(2H,m),1.58-1.74(4H,m),1.90-1.99(2H,m),2.51-2.57(1H,m),2.74(3H,d,J=3.9Hz),2.98-3.17(4H,m),4.01(2H,d,J=13.2Hz),4.63-4.84(2H,m),7.69(1H,s),7.74(1H,s),8.43(1H,d,J=2.4Hz),8.87(1H,d,J=1.9Hz),10.33(1H,brs),12.28(1H,brs),13.00(1H,s).
84	1.52-1.98(12H,m),2.52-2.58(1H,m),3.05(2H,t,J=11.2Hz),3.13-3.24(2H,m),3.30-3.43(2H,m),4.00(2H,d,J=12.7Hz),4.74(2H,d,J=5.4Hz),7.65(1H,s),7.73(1H,s),8.42(1H,d,J=2.0Hz),8.87(1H,d,J=1.9Hz),10.18(1H,brs),12.27(1H,brs),12.99(1H,s).

(Table 27 Continued)

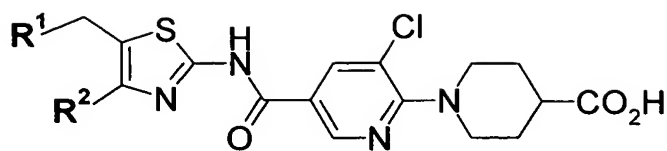
Ex	Data
85	1.48-1.77(10H,m),1.82-1.99(4H,m),2.52-2.59(1H,m),3.05(2H,t,J=11.3Hz),3.16-3.43(4H,m),4.00(2H,d,J=12.7Hz),4.74(2H,d,J=4.9Hz),7.65(1H,d,J=0.9Hz),7.74(1H,d,J=1.0Hz),8.43(1H,d,J=1.5Hz),8.87(1H,d,J=1.9Hz),9.98(1H,brs),12.29(1H,brs),12.99(1H,s).
90	1.03-2.07(14H,m),2.52-2.57(1H,m),2.69(3H,d,J=4.4Hz),3.05(2H,t,J=11.5Hz),3.11-3.22(1H,m),4.01(2H,d,J=13.2Hz),4.58-4.89(2H,m),7.66(1H,s),7.75(1H,s),8.42(1H,d,J=2.0Hz),8.87(1H,d,J=2.0Hz),10.11(1H,brs),12.27(1H,brs),13.01(1H,s).
100	1.60-1.77(4H,m),1.89-2.00(2H,m),2.01-2.20(2H,m),2.18-2.36(2H,m),2.50-2.58(1H,m),2.59-2.63(3H,d,J=4.4Hz),3.05(2H,t,J=11.7Hz),3.72-3.84(1H,m),3.95-4.05(2H,m),4.51-4.62(1H,m),4.65-4.75(1H,m),7.69(1H,s),7.74(1H,s),8.42(1H,d,J=2.2Hz),8.87(1H,d,J=2.2Hz),10.51(1H,brs),12.28(1H,brs),13.02(1H,brs)
101	0.50-1.10(4H,m),1.62-1.75(2H,m),1.89-2.05(2H,m),2.50-2.58(1H,m),2.87(3H,brs),3.05(2H,t,J=11.2Hz),3.11-3.15(1H,m),3.92-4.06(2H,m),4.64-5.08(2H,m),7.62-7.83(2H,m),8.42(1H,d,J=2.0Hz),8.86(1H,d,J=2.0Hz),10.25(1H,brs),12.25(1H,brs),13.00(1H,brs).
104	1.22(3H,d,J=6.9Hz),1.30(3H,d,J=6.8Hz),1.60-1.74(2H,m),1.90-2.00(2H,m),2.50-2.58(1H,m),2.67(3H,d,J=4.9Hz),3.05(2H,t,J=11.3Hz),3.30-3.45(1H,m),4.00(2H,d,J=3.2Hz),4.55-4.65(1H,m),4.72-4.82(1H,m),7.65(1H,s),7.74(1H,d,J=1.5Hz),8.42(1H,d,J=1.9Hz),8.87(1H,d,J=2.0Hz),10.05-10.25(1H,brs),12.97(1H,s).
106	1.42(3H,d,J=6.3Hz),1.61-1.73(3H,m),1.87-1.96(4H,m),2.20-2.23(1H,m),2.49-2.57(1H,m),3.03-3.08(2H,m),3.13-3.22(1H,m),3.48-3.64(2H,m),4.01(2H,d,J=13.2Hz),4.62-4.68(2H,m),4.95(1H,d,J=11.8Hz),7.66(1H,d,J=1.0Hz),7.74(1H,d,J=1.0Hz),8.43(1H,d,J=2.0Hz),8.87(1H,d,J=2.4Hz),10.21(1H,brs),13.01(1H,s).
107	1.42(3H,d,J=6.3Hz),1.61-1.72(3H,m),1.88-1.96(4H,m),2.20-2.28(1H,m),2.49-2.51(1H,m),3.04-3.09(2H,m),3.15-3.20(1H,m),3.42-3.54(2H,m),4.01(2H,d,J=12.7Hz),4.66(1H,d,J=7.8,15.1Hz),4.97(1H,d,J=11.2Hz),7.65(1H,d,J=1.0Hz),7.74(1H,d,J=1.0Hz),8.42(1H,d,J=2.0Hz),8.87(1H,d,J=2.2Hz),9.98(1H,brs),13.01(1H,s).
108	1.05(3H,dd,J=1.5,6.4Hz),1.55-1.72(3H,m),1.90-2.00(2H,m),2.05-2.20(1H,m),2.28-2.40(1H,m),2.50-2.60(1H,m),2.70-2.80(1H,m),3.05(2H,t,J=10.8Hz),3.00-3.60(3H,m),3.95-4.05(2H,d,J=13.2Hz),4.75-4.80(2H,m),7.67-7.69(1H,m),7.72(1H,d,J=1.0Hz),8.43(1H,d,J=1.9Hz),8.83(1H,d,J=1.9Hz),10.75-10.95(1H,brd),12.97(1H,s)..
109	1.05(3H,d,J=6.3Hz),1.64-1.72(3H,m),1.91-1.96(2H,m),2.08-2.33(2H,m),2.50-2.51(1H,m),2.73-2.80(1H,m),3.03-3.08(2H,m),3.25-3.63(3H,m),4.01(2H,d,J=13.2Hz),4.76-4.86(2H,m),7.68(1H,d,J=1.5Hz),7.73(1H,d,J=1.5Hz),8.43(1H,d,J=1.9Hz),8.87(1H,d,J=1.9Hz),10.73(1H,brs),12.99(1H,s).
110	1.05-1.13(3H,m),1.62-1.72(2H,m),1.91-1.98(2H,m),2.50-2.56(1H,m),2.76-2.84(3H,m),3.00-3.10(2H,m),3.30-3.60(5H,m),3.76-3.93(1H,m),3.96-4.40(2H,m),4.62-4.85(2H,m),7.64(1H,d,J=3.9),7.74(1H,s),8.43(1H,d,J=1.9Hz),8.87(1H,d,J=2.0Hz),9.76-10.04(1H,m),13.00(1H,s).
111	1.05-1.13(3H,m),1.62-1.72(2H,m),1.91-1.96(2H,m),2.50-2.55(1H,m),2.76-2.84(3H,m),3.00-3.10(2H,m),3.25-3.60(5H,m),3.76-3.93(1H,m),3.96-4.40(2H,m),4.62-4.85(2H,m),7.61-7.65(1H,m),7.74(1H,s),8.43(1H,d,J=1.9Hz),8.87(1H,d,J=2.4Hz),9.66-9.93(1H,m),12.27(1H,brs),13.01(1H,s).
150	0.87(3H,t,J=7.3Hz),1.17-1.34(4H,m),1.58-1.72(3H,m),1.78(2H,d,J=13.2Hz),2.73(3H,d,J=4.4Hz),2.92(2H,t,J=11.5Hz),2.96-3.18(2H,m),3.31(2H,d,J=6.3Hz),4.11(2H,d,J=12.7Hz),4.62-4.83(2H,m),7.70(1H,s),7.74(1H,s),8.41(1H,d,J=2.0Hz),8.86(1H,d,J=2.0Hz),10.62(1H,brs),12.97(1H,s).

(Table 27 Continued)

Ex	Data
151	0.87(3H,t,J=7.3Hz),1.16-1.34(2H,m),1.57-1.80(4H,m),2.72(3H,d,J=4.4Hz),2.94-3.17(2H,m),3.45-3.60(4H,m),4.60-4.80(2H,m),7.50(1H,brs),7.70(1H,s),7.73(1H,s),8.32(1H,d,J=2.0Hz),8.77(1H,d,J=2.0Hz),10.86(1H,brs),12.79(1H,s).
153	0.87(3H,t,J=7.3Hz),1.18-1.32(2H,m),1.57-1.72(2H,m),2.74(3H,d,J=4.4Hz),2.96-3.19(2H,m),3.32(2H,brs),3.73-4.09(4H,m),4.62-4.84(2H,m),7.70(1H,d,J=1.0Hz),7.74(1H,d,J=1.0Hz),8.07(1H,s),8.48(1H,d,J=2.0Hz),8.89(1H,d,J=2.0Hz),10.39(1H,brs),13.05(1H,s).
221	1.44(3H,d,J=6.3Hz),1.62-1.72(1H,m),1.87-1.97(2H,m),2.18-2.26(1H,m),2.66(2H,d,J=7.4Hz),2.92-2.99(1H,m),3.12-3.20(1H,m),3.49-3.57(3H,m),4.01-4.05(2H,m),4.46(1H,t,8.8Hz),4.62(1H,dd,J=7.3,15.1Hz),4.91(1H,d,J=14.7Hz),.68(1H,d,J=1.0Hz),7.73(1H,d,J=1.4Hz),8.27(1H,d,J=2.0Hz),8.77(1H,d,J=2.0Hz),10.56(1H,brs),12.84(1H,s).
222	1.43(3H,d,J=6.4Hz),1.62-1.71(1H,m),1.87-1.98(2H,m),2.18-2.23(1H,m),2.66(2H,d,J=7.8Hz),2.89-2.99(1H,m),3.12-3.21(1H,m),3.48-3.57(3H,m),4.01-4.05(2H,m),4.43-4.48(1H,m),4.60-4.66(1H,m),4.92(1H,d,J=12.2Hz),7.67(1H,s),7.74(1H,d,J=1.0Hz),8.27(1H,d,J=2.0Hz),8.77(1H,d,J=2.0Hz),10.42(1H,brs),12.84(1H,s).
225	1.42(3H,d,J=6.4Hz),1.60-1.70(1H,m),1.86-1.97(4H,m),2.23-2.26(3H,m),3.13(3H,s),3.15-3.20(1H,m),3.40-3.60(4H,m),4.62-4.67(1H,m),4.95(1H,d,J=15.1Hz),7.65(1H,d,J=0.9Hz),7.74(1H,d,J=1.5Hz),8.38(1H,d,J=1.9Hz),8.82(1H,d,J=2.4Hz),10.08(1H,brs),12.93(1H,s).
226	1.45(3H,d,J=6.3Hz),1.63-1.73(1H,m),1.84-1.97(4H,m),2.18-2.27(3H,m),3.13(3H,s),3.16-3.20(1H,m),3.39-3.59(4H,m),4.63(1H,dd,J=7.3,15.1Hz),4.90(1H,d,J=12.2Hz),7.68(1H,d,J=1.0Hz),7.74(1H,d,J=1.0Hz),8.39(1H,d,J=2.0Hz),8.82(1H,d,J=1.9Hz),10.75(1H,brs),12.92(1H,s).
227	1.22(3H,d,J=6.9Hz),1.32(3H,d,J=6.3Hz),1.84-1.91(2H,m),2.23-2.27(2H,m),2.65(3H,d,J=4.9Hz),3.13(3H,s),3.56-3.61(3H,m),4.58(1H,dd,J=5.9,15.2Hz),4.76(1H,dd,J=3.9,4.7Hz),.67(1H,s),7.74(1H,s),8.39(1H,d,J=2.0Hz),8.82(1H,d,J=1.9Hz),10.57(1H,brs),12.91(1H,s).
271	1.19(3H,d,J=6.9Hz),1.30(3H,d,J=6.3Hz),1.60-1.72(2H,m),1.90-1.98(2H,m),2.28(3H,s),2.52-2.58(1H,m),2.65(3H,d,J=5.3Hz),3.05(2H,t,J=11.2Hz),3.52-3.64(1H,m),4.00(2H,d,J=13.2Hz),4.55-4.80(2H,m),7.30(1H,s),7.40(1H,s),8.42(1H,d,J=2.5Hz),8.75(1H,d,J=2.0Hz),9.80-9.90(1H,brs),12.97(1H,s).
314	1.45(3H,d,J=6.3Hz),1.55-1.72(3H,m),1.90-2.00(4H,m),2.15-2.25(1H,m),2.55-2.65(1H,m),3.20-3.32(3H,m),3.45-3.55(2H,m),4.45(2H,d,J=13.2Hz),4.59-4.67(1H,m),4.85-4.95(1H,m),7.69(1H,d,J=1.5Hz),7.72(1H,d,J=1.4Hz),8.14(1H,dd,J=1.9,15.1Hz),8.75(1H,t,J=0.9Hz),10.75(1H,brs),12.90(1H,s).
315	1.42(3H,d,J=6.4Hz),1.55-1.70(3H,m),1.85-2.00(4H,m),2.15-2.25(1H,m),2.54-2.65(1H,m),3.10-3.22(3H,m),3.45-3.60(2H,m),4.23(2H,d,J=13.2Hz),4.55-4.65(1H,m),4.85-4.95(1H,m),7.65(1H,d,J=1.0Hz),7.75(1H,s),8.13(1H,dd,J=2.0,15.1Hz),8.75(1H,s),10.67(1H,brs),12.90(1H,s).

Structures of the other compounds of the present invention are shown in Tables 28 to 41 below. They can be produced easily by using the methods described in production examples and examples, or methods obvious to one skilled in the art, or modifications thereof.

(Table 28)



No	R ¹	R ²	No	R ¹	R ²
A1	EtN(Me)-	4-Cl-2-The	A40	2-Me-pyrr	4-Cl-2-The
A2	nPrN(Me)-	4-Cl-2-The	A41	3-Me-pyrr	4-Cl-2-The
A3	iPrN(Me)-	4-Cl-2-The	A42	3,4-diMe-pyrr	4-Cl-2-The
A4	iBuN(Me)-	4-Cl-2-The	A43	3,3-diMe-pyrr	4-Cl-2-The
A5	sBuN(Me)-	4-Cl-2-The	A44	2-Me-pipe	4-Cl-2-The
A6	tBuN(Me)-	4-Cl-2-The	A45	3-Me-pipe	4-Cl-2-The
A7	tBuCH ₂ N(Me)-	4-Cl-2-The	A46	4-Me-pipe	4-Cl-2-The
A8	cPenN(Me)-	4-Cl-2-The	A47	3,3-diMe-pipe	4-Cl-2-The
A9	cPrCH ₂ N(Me)-	4-Cl-2-The	A48	4,4-diMe-pipe	4-Cl-2-The
A10	cBuCH ₂ N(Me)-	4-Cl-2-The	A49	EtN(Me)-	4-Me-2-The
A11	MeO H(Me)CH ₂ N(Me)-	4-Cl-2-The	A50	nPrN(Me)-	4-Me-2-The
A12	nPrN(Et)-	4-Cl-2-The	A51	sBuN(Me)-	4-Me-2-The
A13	nBuN(Et)-	4-Cl-2-The	A52	tBuN(Me)-	4-Me-2-The
A14	iPrN(Et)-	4-Cl-2-The	A53	tBuCH ₂ N(Me)-	4-Me-2-The
A15	iBuN(Et)-	4-Cl-2-The	A54	cPrN(Me)-	4-Me-2-The
A16	sBuN(Et)-	4-Cl-2-The	A55	cPenN(Me)-	4-Me-2-The
A17	tBuN(Et)-	4-Cl-2-The	A56	cPrCH ₂ N(Me)-	4-Me-2-The
A18	tBuCH ₂ N(Et)-	4-Cl-2-The	A57	cBuCH ₂ N(Me)-	4-Me-2-The
A19	cPrN(Et)-	4-Cl-2-The	A58	MeO(CH ₂) ₂ N(Me)-	4-Me-2-The
A20	cBuN(Et)-	4-Cl-2-The	A59	MeOCH ₂ CH(Me)N(Me)-	4-Me-2-The
A21	cPenN(Et)-	4-Cl-2-The	A60	MeOCH(Me)CH ₂ N(Me)-	4-Me-2-The
A22	cHexN(Et)-	4-Cl-2-The	A61	EtO(CH ₂) ₂ N(Me)-	4-Me-2-The
A23	cPrCH ₂ N(Et)-	4-Cl-2-The	A62	nPrO(CH ₂) ₂ N(Me)-	4-Me-2-The
A24	cBuCH ₂ N(Et)-	4-Cl-2-The	A63	iPrO(CH ₂) ₂ N(Me)-	4-Me-2-The
A25	MeO(CH ₂) ₂ N(Et)-	4-Cl-2-The	A64	MeO(CH ₂) ₃ N(Me)-	4-Me-2-The
A26	MeOCH ₂ CH(Me)N(Et)-	4-Cl-2-The	A65	Et ₂ N-	4-Me-2-The
A27	MeOCH(Me)CH ₂ N(Et)-	4-Cl-2-The	A66	nPrN(Et)-	4-Me-2-The
A28	(MeO(CH ₂) ₂) ₂ N-	4-Cl-2-The	A67	nBuN(Et)-	4-Me-2-The
A29	MeO(CH ₂) ₂ -N(cPr)-	4-Cl-2-The	A68	iPrN(Et)-	4-Me-2-The
A30	MeO(CH ₂) ₂ -N(cBu)-	4-Cl-2-The	A69	iBuN(Et)-	4-Me-2-The
A31	EtO(CH ₂) ₂ N(Et)-	4-Cl-2-The	A70	sBuN(Et)-	4-Me-2-The
A32	nPrO(CH ₂) ₂ N(Et)-	4-Cl-2-The	A71	tBuN(Et)-	4-Me-2-The
A33	iPrO(CH ₂) ₂ N(Et)-	4-Cl-2-The	A72	tBuCH ₂ N(Et)-	4-Me-2-The
A34	MeO(CH ₂) ₃ N(Et)-	4-Cl-2-The	A73	cPrN(Et)-	4-Me-2-The
A35	2-Me-azet	4-Cl-2-The	A74	cBuN(Et)-	4-Me-2-The
A36	3-Me-azet	4-Cl-2-The	A75	cPenN(Et)-	4-Me-2-The
A37	3,3-diMe-azet	4-Cl-2-The	A76	cHexN(Et)-	4-Me-2-The
A38	cPrCH ₂ N(Et)-	4-Me-2-The	A77	MeO(CH ₂) ₂ N(Me)-	4-Br-2-The
A39	cBuCH ₂ N(Et)-	4-Me-2-The	A78	pipe	4-Br-2-The

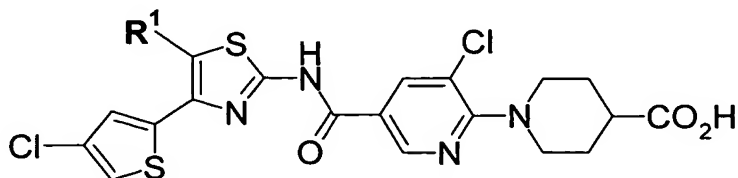
(Table 28 Continued)

No	R ¹	R ²	No	R ¹	R ²
A79	MeO(CH ₂) ₂ N(Et)-	4-Me-2-The	A123	Me ₂ N-	4-F-2-The
A80	MeOCH ₂ CH(Me)N(Et)-	4-Me-2-The	A124	nBuN(Me)-	4-F-2-The
A81	MeOCH(Me)CH ₂ N(Et)-	4-Me-2-The	A125	cHexN(Me)-	4-F-2-The
A82	EtO(CH ₂) ₂ N(Et)-	4-Me-2-The	A126	MeO(CH ₂) ₂ N(Me)-	4-F-2-The
A83	nPrO(CH ₂) ₂ N(Et)-	4-Me-2-The	A127	pipe	4-F-2-The
A84	iPrO(CH ₂) ₂ N(Et)-	4-Me-2-The	A128	Me ₂ N-	4-Et-2-The
A85	MeO(CH ₂) ₃ N(Et)-	4-Me-2-The	A129	nBuN(Me)-	4-Et-2-The
A86	azet	4-Me-2-The	A130	cHexN(Me)-	4-Et-2-The
A87	pyrr	4-Me-2-The	A131	MeO(CH ₂) ₂ N(Me)-	4-Et-2-The
A88	pipe	4-Me-2-The	A132	pipe	4-Et-2-The
A89	Azepan-1-yl	4-Me-2-The	A133	Me ₂ N-	5-Cl-2-The
A90	Azocan-1-yl	4-Me-2-The	A134	nBuN(Me)-	5-Cl-2-The
A91	2-Me-azet	4-Me-2-The	A135	cHexN(Me)-	5-Cl-2-The
A92	3-Me-azet	4-Me-2-The	A136	MeO(CH ₂) ₂ N(Me)-	5-Cl-2-The
A93	3,3-diMe-azet	4-Me-2-The	A137	pipe	5-Cl-2-The
A94	2-Me-pyrr	4-Me-2-The	A138	Me ₂ N-	4-F-Ph
A95	3-Me-pyrr	4-Me-2-The	A139	cHexN(Me)-	4-F-Ph
A96	3,4-diMe-pyrr	4-Me-2-The	A140	MeO(CH ₂) ₂ N(Me)-	4-F-Ph
A97	3,3-diMe-pyrr	4-Me-2-The	A141	Me ₂ N-	3-Cl-Ph
A98	2-Me-pipe	4-Me-2-The	A142	nBuN(Me)-	3-Cl-Ph
A99	3-Me-pipe	4-Me-2-The	A143	cHex(Me)-	3-Cl-Ph
A100	4-Me-pipe	4-Me-2-The	A144	MeO(CH ₂) ₂ N(Me)-	3-Cl-Ph
A101	3,3-diMe-pipe	4-Me-2-The	A145	pipe	3-Cl-Ph
A102	4,4-diMe-pipe	4-Me-2-The	A146	Me ₂ N-	3-F ₃ C-Ph
A103	Me ₂ N-	4-Br-2-The	A147	nBuN(Me)-	3-F ₃ C-Ph
A104	nBuN(Me)-	4-Br-2-The	A148	cHexN(Me)-	3-F ₃ C-Ph
A105	cHexN(Me)-	4-Br-2-The	A149	MeO(CH ₂) ₂ N(Me)-	3-F ₃ C-Ph
A106	2-Et-azet	4-Cl-2-The	A150	2-Et-azet	4-Me-2-The
A107	3-Et-azet	4-Cl-2-The	A151	3-Et-azet	4-Me-2-The
A108	2-Et-pyrr	4-Cl-2-The	A152	2-Et-pyrr	4-Me-2-The
A109	3-Et-pyrr	4-Cl-2-The	A153	3-Et-pyrr	4-Me-2-The
A110	2-Et-pipe	4-Cl-2-The	A154	2-Et-pipe	4-Me-2-The
A111	3-Et-pipe	4-Cl-2-The	A155	3-Et-pipe	4-Me-2-The
A112	4-Et-pipe	4-Cl-2-The	A156	4-Et-pipe	4-Me-2-The
A113	2-MeOCH ₂ -azet	4-Cl-2-The	A157	2-MeOCH ₂ -azet	4-Me-2-The
A114	3-MeOCH ₂ -azet	4-Cl-2-The	A158	3-MeOCH ₂ -azet	4-Me-2-The
A115	2-MeOCH ₂ -pyrr	4-Cl-2-The	A159	2-MeOCH ₂ -pyrr	4-Me-2-The
A116	3-MeOCH ₂ -pyrr	4-Cl-2-The	A160	3-MeOCH ₂ -pyrr	4-Me-2-The
A117	2-MeOCH ₂ -pipe	4-Cl-2-The	A161	2-MeOCH ₂ -pipe	4-Me-2-The
A118	3-MeOCH ₂ -pipe	4-Cl-2-The	A162	3-MeOCH ₂ -pipe	4-Me-2-The
A119	4-MeOCH ₂ -pipe	4-Cl-2-The	A163	4-MeOCH ₂ -pipe	4-Me-2-The
A120	3-MeO-azet	4-Cl-2-The	A164	3-MeO-azet	4-Me-2-The
A121	3-MeO-pyrr	4-Cl-2-The	A165	3-MeO-pyrr	4-Me-2-The
A122	3-MeO-pipe	4-Cl-2-The	A166	3-MeO-pipe	4-Me-2-The

(Table 28 Continued)

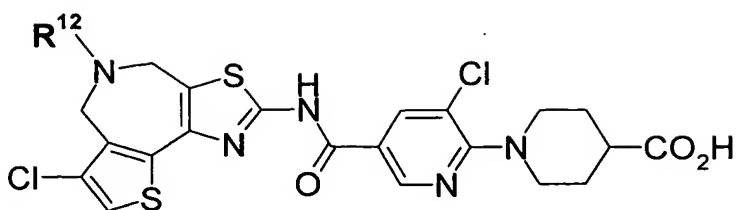
No	R ¹	R ²	No	R ¹	R ²
A167	4-MeO-pipe	4-Cl-2-The	A172	4-MeO-pipe	4-Me-2-The
A168	3-F-azet	4-Cl-2-The	A173	3-F-azet	4-Me-2-The
A169	3-F-pyrr	4-Cl-2-The	A174	3-F-pyrr	4-Me-2-The
A170	3-F-pipe	4-Cl-2-The	A175	3-F-pipe	4-Me-2-The
A171	4-F-pipe	4-Cl-2-The	A176	4-F-pipe	4-Me-2-The

(Table 29)



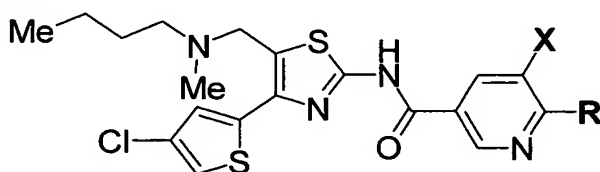
No	R ¹	No	R ¹
B1	Me ₂ NCH(Me)-	B15	MeO(CH ₂) ₂ N(Me)-(CH ₂) ₃ -
B2	Me ₂ NC(Me) ₂ -	B16	pipe-CH(Me)-
B3	Me ₂ N(CH ₂) ₂ -	B17	pipe-C(Me) ₂ -
B4	Me ₂ N(CH ₂) ₃ -	B18	pipe-(CH ₂) ₂ -
B5	nBuN(Me)-CH(Me)-	B19	pipe-(CH ₂) ₃ -
B6	nBuN(Me)-C(Me) ₂ -	B20	(Azepan-1-yl)-CH(Me)-
B7	nBuN(Me)-(CH ₂) ₃ -	B21	(Azepan-1-yl)-C(Me) ₂ -
B8	cHexN(Me)-CH(Me)-	B22	(Azepan-1-yl)-(CH ₂) ₂ -
B9	cHexN(Me)-C(Me) ₂ -	B23	(Azepan-1-yl)-(CH ₂) ₃ -
B10	cHexN(Me)-(CH ₂) ₂ -	B24	(Azocan-1-yl)-CH(Me)-
B11	cHexN(Me)-(CH ₂) ₃ -	B25	(Azocan-1-yl)-C(Me) ₂ -
B12	MeO(CH ₂) ₂ N(Me)-CH(Me)-	B26	(Azocan-1-yl)-(CH ₂) ₂ -
B13	MeO(CH ₂) ₂ N(Me)-C(Me) ₂ -	B27	(Azocan-1-yl)-(CH ₂) ₃ -
B14	MeO(CH ₂) ₂ N(Me)-(CH ₂) ₂ -		

(Table 30)



No	R ¹²	No	R ¹²	No	R ¹²
C1	Me	C8	tBuCH ₂ -	C15	MeOCH ₂ CH(Me) -
C2	Et	C9	cPr	C16	MeO CH(Me)CH ₂ -
C3	nPr	C10	cBu	C17	EtO(CH ₂) ₂ -
C4	iPr	C11	cPen	C18	nPrO(CH ₂) ₂ -
C5	iBu	C12	cHex	C19	iPrO(CH ₂) ₂ -
C6	sBu	C13	cPrCH ₂ -	C20	MeO(CH ₂) ₃ -
C7	tBu	C14	cBuCH ₂ -		

(Table 31)



No	X	R	No	X	R
D1	Cl	3-HO ₂ C-pipe	D21	Cl	HO ₂ C(CH ₂) ₃ N(Me)-
D2	Cl	4- HO ₂ CCH ₂ -pipe	D22	Cl	HO ₂ C(CH ₂) ₂ N(Me)-
D3	Cl	4-HO ₂ CCH ₂ -pipa	D23	Cl	HO ₂ CCH ₂ N(Me)-
D4	Cl	3-HO ₂ CCH ₂ -pyrr	D24	Cl	HO ₂ C(CH ₂) ₃ O-
D5	Cl	3-HO ₂ CCH ₂ -azet	D25	Cl	HO ₂ C(CH ₂) ₂ O-
D6	Cl	4-HO-pipe	D26	Cl	HO ₂ CCH ₂ O-
D7	Cl	3-HO-pipe	D27	F	4-HO ₂ C-pipe
D8	Cl	3-HO-pyrr	D28	F	3-HO ₂ C-pipe
D9	Cl	4-HOCH ₂ -pipe	D29	F	3-HO ₂ C-pyrr
D10	Cl	3-HO-4-HO ₂ C-pipe	D30	F	4-HO ₂ CCH ₂ -pipe
D11	Cl	4-HO-4-HO ₂ C-pipe	D31	F	4-HO ₂ CCH ₂ -pipa
D12	Cl	4-HO-4-HO ₂ CCH ₂ -pipe	D32	F	3-HO ₂ CCH ₂ -pyrr
D13	Cl	4- HO ₂ CCH(OH)-pipe	D33	F	3-HO ₂ CCH ₂ -azet
D14	Cl	HO(CH ₂) ₂ NH-	D34	F	4-HO-pipe
D15	Cl	HO(CH ₂) ₃ N(Me)-	D35	F	3-HO-pipe
D16	Cl	HO(CH ₂) ₂ N(Me)-	D36	F	3-HO-pyrr
D17	Cl	HO(CH ₂) ₃ O-	D37	F	4-HOCH ₂ -pipe
D18	Cl	HO(CH ₂) ₂ O-	D38	F	4-HO ₂ CCH ₂ O-pipe
D19	Cl	HO ₂ C(CH ₂) ₂ NH-	D39	F	3-HO-4-HO ₂ C-pipe
D20	Cl	HO ₂ CCH ₂ NH-	D40	F	4-HO-4-HO ₂ C-pipe

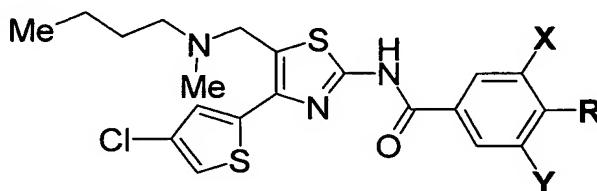
(Table 31 Continued)

No	X	R	No	X	R
D41	F	4-HO-4-HO ₂ CCH ₂ -pipe	D85	F	HO ₂ C(CH ₂) ₂ NH-
D42	F	4- HO ₂ CCH(OH)-pipe	D86	F	HO ₂ CCH ₂ NH-
D43	F	HO(CH ₂) ₃ NH-	D87	F	HO ₂ C(CH ₂) ₃ N(Me)-
D44	F	HO(CH ₂) ₂ NH-	D88	F	HO ₂ C(CH ₂) ₂ N(Me)-
D45	F	HO(CH ₂) ₃ N(Me)-	D89	F	HO ₂ CCH ₂ N(Me)-
D46	F	HO(CH ₂) ₂ N(Me)-	D90	F	HO ₂ C(CH ₂) ₃ O-
D47	F	HO(CH ₂) ₃ O-	D91	F	HO ₂ C(CH ₂) ₂ O-
D48	F	HO(CH ₂) ₂ O-	D92	F	HO ₂ CCH ₂ O-
D49	F	HO ₂ C(CH ₂) ₃ NH-	D93	Me	4-HO ₂ C-pipe
D50	H	4-HO ₂ C-pipe	D94	Me	3-HO ₂ C-pipe
D51	H	3-HO ₂ C-pipe	D95	Me	3-HO ₂ C-pyrr
D52	H	3-HO ₂ C-pyrr	D96	Me	3-HO ₂ C-azet
D53	H	3-HO ₂ C-azet	D97	Me	4- HO ₂ CCH ₂ -pipe
D54	H	4- HO ₂ CCH ₂ -pipe	D98	Me	4-HO ₂ CCH ₂ -pipa
D55	H	4-HO ₂ CCH ₂ -pipa	D99	Me	3-HO ₂ CCH ₂ -pyrr
D56	H	3-HO ₂ CCH ₂ -pyrr	D100	Me	3-HO ₂ CCH ₂ -azet
D57	H	3-HO ₂ CCH ₂ -azet	D101	Me	HO ₂ C(CH ₂) ₃ NH-
D58	H	HO ₂ C(CH ₂) ₃ NH-	D102	Me	HO ₂ C(CH ₂) ₂ NH-
D59	H	HO ₂ C(CH ₂) ₂ NH-	D103	Me	HO ₂ CCH ₂ NH-
D60	H	HO ₂ CCH ₂ NH-	D104	Me	HO ₂ C(CH ₂) ₃ N(Me)-
D61	H	HO ₂ C(CH ₂) ₃ N(Me)-	D105	Me	HO ₂ C(CH ₂) ₂ N(Me)-
D62	H	HO ₂ C(CH ₂) ₂ N(Me)-	D106	Me	HO ₂ CCH ₂ N(Me)-
D63	H	HO ₂ CCH ₂ N(Me)-	D107	Me	HO ₂ C(CH ₂) ₃ O-
D64	H	HO ₂ C(CH ₂) ₃ O-	D108	Me	HO ₂ C(CH ₂) ₂ O-
D65	H	HO ₂ C(CH ₂) ₂ O-	D109	Me	HO ₂ CCH ₂ O-
D66	H	HO ₂ CCH ₂ O-	D110	MeO	4-HO ₂ C-pipe
D67	Br	4-HO ₂ C-pipe	D111	MeO	3-HO ₂ C-pipe
D68	Br	3-HO ₂ C-pipe	D112	MeO	3-HO ₂ C-pyrr
D69	Br	3-HO ₂ C-pyrr	D113	MeO	3-HO ₂ C-azet
D70	Br	3-HO ₂ C-azet	D114	MeO	4- HO ₂ CCH ₂ -pipe
D71	Br	4-HO ₂ CCH ₂ -pipe	D115	MeO	4-HO ₂ CCH ₂ -pipa
D72	Br	4-HO ₂ CCH ₂ -pipa	D116	MeO	3-HO ₂ CCH ₂ -pyrr
D73	Br	3-HO ₂ CCH ₂ -pyrr	D117	MeO	3-HO ₂ CCH ₂ -azet
D74	Br	3-HO ₂ CCH ₂ -azet	D118	MeO	HO ₂ C(CH ₂) ₃ NH-
D75	Br	HO ₂ C(CH ₂) ₃ NH-	D119	MeO	HO ₂ C(CH ₂) ₂ NH-
D76	Br	HO ₂ C(CH ₂) ₂ NH-	D120	MeO	HO ₂ CCH ₂ NH-
D77	Br	HO ₂ CCH ₂ NH-	D121	CF ₃	3-HO ₂ C-pipe
D78	Br	HO ₂ C(CH ₂) ₃ N(Me)-	D122	CF ₃	3-HO ₂ C-pyrr
D79	Br	HO ₂ C(CH ₂) ₂ N(Me)-	D123	CF ₃	3-HO ₂ C-azet
D80	Br	HO ₂ CCH ₂ N(Me)-	D124	CF ₃	4- HO ₂ CCH ₂ -pipe
D81	Br	HO ₂ C(CH ₂) ₃ O-	D125	CF ₃	4-HO ₂ CCH ₂ -pipa
D82	Br	HO ₂ C(CH ₂) ₂ O-	D126	CF ₃	3-HO ₂ CCH ₂ -pyrr
D83	Br	HO ₂ CCH ₂ O-	D127	CF ₃	3-HO ₂ CCH ₂ -azet
D84	CF ₃	4-HO ₂ C-pipe	D128	CF ₃	HO ₂ C(CH ₂) ₃ NH-

(Table 31 Continued)

No	X	R	No	X	R
D129	CF ₃	HO ₂ C(CH ₂) ₂ NH-	D137	MeO	HO ₂ C(CH ₂) ₃ N(Me)-
D130	CF ₃	HO ₂ CCH ₂ NH-	D138	MeO	HO ₂ C(CH ₂) ₂ N(Me)-
D131	CF ₃	HO ₂ C(CH ₂) ₃ N(Me)-	D139	MeO	HO ₂ CCH ₂ N(Me)-
D132	CF ₃	HO ₂ C(CH ₂) ₂ N(Me)-	D140	MeO	HO ₂ C(CH ₂) ₃ O-
D133	CF ₃	HO ₂ CCH ₂ N(Me)-	D141	MeO	HO ₂ C(CH ₂) ₂ O-
D134	CF ₃	HO ₂ C(CH ₂) ₃ O-	D142	MeO	HO ₂ CCH ₂ O-
D135	CF ₃	HO ₂ C(CH ₂) ₂ O-	D143	Cl	3-HO ₂ C-azet
D136	CF ₃	HO ₂ CCH ₂ O-	D144	F	3-HO ₂ C-azet

(Table 32)



No	X	Y	R	No	X	Y	R
E1	F	H	HO(CH ₂) ₃ NH-	E27	F	F	HO(CH ₂) ₂ NH-
E2	F	H	HO(CH ₂) ₂ NH-	E28	F	F	HO(CH ₂) ₃ N(Me)-
E3	F	H	HO(CH ₂) ₃ N(Me)-	E29	F	F	HO(CH ₂) ₂ N(Me)-
E4	F	H	HO(CH ₂) ₂ N(Me)-	E30	F	F	HO(CH ₂) ₃ O-
E5	F	H	HO(CH ₂) ₃ O-	E31	F	F	HO(CH ₂) ₂ O-
E6	F	H	HO(CH ₂) ₂ O-	E32	F	F	HO ₂ C(CH ₂) ₃ NH-
E7	F	H	HO ₂ C(CH ₂) ₃ NH-	E33	F	F	HO ₂ C(CH ₂) ₂ NH-
E8	F	H	HO ₂ C(CH ₂) ₂ NH-	E34	F	F	HO ₂ CCH ₂ NH-
E9	F	H	HO ₂ CCH ₂ NH-	E35	F	F	HO ₂ C(CH ₂) ₃ N(Me)-
E10	F	H	HO ₂ C(CH ₂) ₃ N(Me)-	E36	F	F	HO ₂ C(CH ₂) ₂ N(Me)-
E11	F	H	HO ₂ C(CH ₂) ₂ N(Me)-	E37	F	F	HO ₂ CCH ₂ N(Me)-
E12	F	H	HO ₂ CCH ₂ N(Me)-	E38	F	F	HO ₂ C(CH ₂) ₃ O-
E13	F	H	HO ₂ C(CH ₂) ₂ O-	E39	F	F	HO ₂ C(CH ₂) ₂ O-
E14	F	H	HO ₂ CCH ₂ O-	E40	F	F	HO ₂ CCH ₂ O-
E15	Cl	H	HO(CH ₂) ₃ NH-	E41	Cl	F	HO(CH ₂) ₃ NH-
E16	Cl	H	HO(CH ₂) ₂ NH-	E42	Cl	F	HO(CH ₂) ₂ NH-
E17	Cl	H	HO(CH ₂) ₃ N(Me)-	E43	Cl	F	HO(CH ₂) ₃ N(Me)-
E18	Cl	H	HO(CH ₂) ₂ N(Me)-	E44	Cl	F	HO(CH ₂) ₂ N(Me)-
E19	Cl	H	HO(CH ₂) ₃ O-	E45	Cl	F	HO(CH ₂) ₃ O-
E20	Cl	H	HO(CH ₂) ₂ O-	E46	Cl	F	HO(CH ₂) ₂ O-
E21	Cl	H	HO ₂ C(CH ₂) ₃ NH-	E47	Cl	F	HO ₂ C(CH ₂) ₃ NH-
E22	Cl	H	HO ₂ C(CH ₂) ₂ NH-	E48	Cl	F	HO ₂ C(CH ₂) ₂ NH-
E23	Cl	H	HO ₂ CCH ₂ NH-	E49	Cl	F	HO ₂ CCH ₂ NH-
E24	Cl	H	HO ₂ C(CH ₂) ₃ N(Me)-	E50	Cl	F	HO ₂ C(CH ₂) ₃ N(Me)-
E25	Cl	H	HO ₂ C(CH ₂) ₂ N(Me)-	E51	Cl	F	HO ₂ C(CH ₂) ₂ N(Me)-
E26	Cl	H	HO ₂ CCH ₂ N(Me)-	E52	Cl	F	HO ₂ CCH ₂ N(Me)-

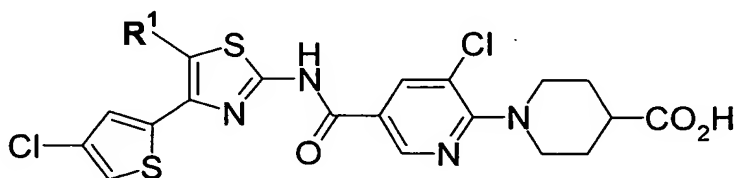
(Table 32 Continued)

No	X	Y	R	No	X	Y	R
E53	Cl	H	HO ₂ C(CH ₂) ₃ O-	E97	Cl	F	HO ₂ C(CH ₂) ₃ O-
E54	Cl	H	HO ₂ C(CH ₂) ₂ O-	E98	Cl	F	HO ₂ C(CH ₂) ₂ O-
E55	Cl	H	HO ₂ CCH ₂ O-	E99	Cl	F	HO ₂ CCH ₂ O-
E56	F	F	HO(CH ₂) ₃ NH-	E100	Me	H	4-HO ₂ C-pipe
E57	H	H	4-HO ₂ C-pipe	E101	Me	H	3-HO ₂ C-pipe
E58	H	H	3-HO ₂ C-pipe	E102	Me	H	3-HO ₂ C-pyrr
E59	H	H	3-HO ₂ C-pyrr	E103	Me	H	3-HO ₂ C-azet
E60	H	H	3-HO ₂ C-azet	E104	Me	H	4- HO ₂ CCH ₂ -pipe
E61	H	H	4- HO ₂ CCH ₂ -pipe	E105	Me	H	4-HO ₂ CCH ₂ -pipa
E62	H	H	4-HO ₂ CCH ₂ -pipa	E106	Me	H	3-HO ₂ CCH ₂ -pyrr
E63	H	H	3-HO ₂ CCH ₂ -pyrr	E107	Me	H	3-HO ₂ CCH ₂ -azet
E64	H	H	3-HO ₂ CCH ₂ -azet	E108	Me	H	HO ₂ C(CH ₂) ₃ NH-
E65	H	H	HO ₂ C(CH ₂) ₃ NH-	E109	Me	H	HO ₂ C(CH ₂) ₂ NH-
E66	H	H	HO ₂ C(CH ₂) ₂ NH-	E110	Me	H	HO ₂ CCH ₂ NH-
E67	H	H	HO ₂ CCH ₂ NH-	E111	Me	H	HO ₂ C(CH ₂) ₃ N(Me)-
E68	H	H	HO ₂ C(CH ₂) ₃ N(Me)-	E112	Me	H	HO ₂ C(CH ₂) ₂ N(Me)-
E69	H	H	HO ₂ C(CH ₂) ₂ N(Me)-	E113	Me	H	HO ₂ CCH ₂ N(Me)-
E70	H	H	HO ₂ CCH ₂ N(Me)-	E114	Me	H	HO ₂ C(CH ₂) ₃ O-
E71	H	H	HO ₂ C(CH ₂) ₃ O-	E115	Me	H	HO ₂ C(CH ₂) ₂ O-
E72	H	H	HO ₂ C(CH ₂) ₂ O-	E116	Me	H	HO ₂ CCH ₂ O-
E73	H	H	HO ₂ CCH ₂ O-	E117	MeO	H	4-HO ₂ C-pipe
E74	Br	H	4-HO ₂ C-pipe	E118	MeO	H	3-HO ₂ C-pipe
E75	Br	H	3-HO ₂ C-pipe	E119	MeO	H	3-HO ₂ C-pyrr
E76	Br	H	3-HO ₂ C-pyrr	E120	MeO	H	3-HO ₂ C-azet
E77	Br	H	3-HO ₂ C-azet	E121	MeO	H	4- HO ₂ CCH ₂ -pipe
E78	Br	H	4- HO ₂ CCH ₂ -pipe	E122	MeO	H	4-HO ₂ CCH ₂ -pipa
E79	Br	H	4-HO ₂ CCH ₂ -pipa	E123	MeO	H	3-HO ₂ CCH ₂ -pyrr
E80	Br	H	3-HO ₂ CCH ₂ -pyrr	E124	MeO	H	3-HO ₂ CCH ₂ -azet
E81	Br	H	3-HO ₂ CCH ₂ -azet	E125	MeO	H	HO ₂ C(CH ₂) ₃ NH-
E82	Br	H	HO ₂ C(CH ₂) ₃ NH-	E126	MeO	H	HO ₂ C(CH ₂) ₂ NH-
E83	Br	H	HO ₂ C(CH ₂) ₂ NH-	E127	MeO	H	HO ₂ CCH ₂ NH-
E84	Br	H	HO ₂ CCH ₂ NH-	E128	MeO	H	HO ₂ C(CH ₂) ₃ N(Me)-
E85	Br	H	HO ₂ C(CH ₂) ₃ N(Me)-	E129	MeO	H	HO ₂ C(CH ₂) ₂ N(Me)-
E86	Br	H	HO ₂ C(CH ₂) ₂ N(Me)-	E130	MeO	H	HO ₂ CCH ₂ N(Me)-
E87	Br	H	HO ₂ CCH ₂ N(Me)-	E131	MeO	H	HO ₂ C(CH ₂) ₃ O-
E88	Br	H	HO ₂ C(CH ₂) ₃ O-	E132	MeO	H	HO ₂ C(CH ₂) ₂ O-
E89	Br	H	HO ₂ C(CH ₂) ₂ O-	E133	MeO	H	HO ₂ CCH ₂ O-
E90	Br	H	HO ₂ CCH ₂ O-	E134	Cl	H	4-HO ₂ C-pipe
E91	CF ₃	H	4-HO ₂ C-pipe	E135	Cl	H	3-HO ₂ C-pipe
E92	CF ₃	H	3-HO ₂ C-pipe	E136	Cl	H	3-HO ₂ C-pyrr
E93	CF ₃	H	3-HO ₂ C-pyrr	E137	Cl	H	3-HO ₂ C-azet
E94	CF ₃	H	3-HO ₂ C-azet	E138	Cl	H	4- HO ₂ CCH ₂ -pipe
E95	CF ₃	H	4- HO ₂ CCH ₂ -pipe	E139	Cl	H	4-HO ₂ CCH ₂ -pipa
E96	CF ₃	H	4-HO ₂ CCH ₂ -pipa	E140	Cl	H	3-HO ₂ CCH ₂ -pyrr

(Table 32 Continued)

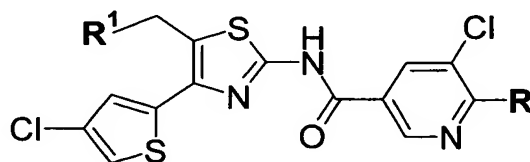
No	X	Y	R	No	X	Y	R
E141	CF ₃	H	3-HO ₂ CCH ₂ -pyrr	E151	Cl	H	3-HO ₂ CCH ₂ -azet
E142	CF ₃	H	3-HO ₂ CCH ₂ -azet	E152	F	H	4-HO ₂ C-pipe
E143	CF ₃	H	HO ₂ C(CH ₂) ₃ NH-	E153	F	H	3-HO ₂ C-pipe
E144	CF ₃	H	HO ₂ C(CH ₂) ₂ NH-	E154	F	H	3-HO ₂ C-pyrr
E145	CF ₃	H	HO ₂ CCH ₂ NH-	E155	CF ₃	H	HO ₂ C(CH ₂) ₃ N(Me)-
E146	CF ₃	H	HO ₂ C(CH ₂) ₂ N(Me)-	E156	F	H	3-HO ₂ C-azet
E147	CF ₃	H	HO ₂ CCH ₂ N(Me)-	E157	F	H	4-HO ₂ CCH ₂ -pipe
E148	CF ₃	H	HO ₂ C(CH ₂) ₃ O-	E158	F	H	4-HO ₂ CCH ₂ -pipa
E149	CF ₃	H	HO ₂ C(CH ₂) ₂ O-	E159	F	H	3-HO ₂ CCH ₂ -pyrr
E150	CF ₃	H	HO ₂ CCH ₂ O-	E160	F	H	3-HO ₂ CCH ₂ -azet

(Table 33)



No	R ¹	No	R ¹
F1	1-Me-piperidin-2-yl	F8	1-Me-4-F-piperidin-2-yl
F2	1-Me-pyrrolidin-2-yl	F9	1,5-diMe-piperidin-2-yl
F3	1-Me-azepan-2-yl	F10	1-Me-5-nPr-piperidin-2-yl
F4	1-Et-piperidin-2-yl	F11	1-Me-5-nPrO-piperidin-2-yl
F5	1,4-diMe-piperidin-2-yl	F12	1-Me-5-F-piperidin-2-yl
F6	1-Me-4-nPr-piperidin-2-yl	F13	1,6-diMe-piperidin-2-yl
F7	1-Me-4-nPrO-piperidin-2-yl	F14	1-Me-6-nPr-piperidin-2-yl

(Table 34)

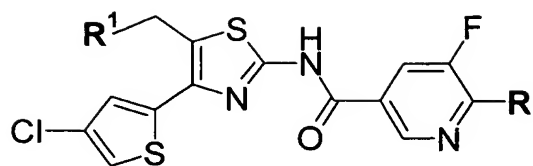


No	R ¹	R	No	R ¹	R
G1	2-Me-pyrr	4-HO ₂ C-pipe	G9	3-Me-pyrr	4-HO ₂ C-pipe
G2	2-Me-pyrr	3-HO ₂ C-pipe	G10	3-Me-pyrr	3-HO ₂ C-pipe
G3	2-Me-pyrr	3-HO ₂ C-pyrr	G11	3-Me-pyrr	3-HO ₂ C-pyrr
G4	2-Me-pyrr	3-HO ₂ C-azet	G12	3-Me-pyrr	3-HO ₂ C-azet
G5	2-Me-pyrr	4-HO ₂ CCH ₂ -pipe	G13	3-Me-pyrr	4-HO ₂ CCH ₂ -pipe
G6	2-Me-pyrr	4-HO ₂ CCH ₂ -pipa	G14	3-Me-pyrr	4-HO ₂ CCH ₂ -pipa
G7	2-Me-pyrr	3-HO ₂ CCH ₂ -pyrr	G15	3-Me-pyrr	3-HO ₂ CCH ₂ -pyrr
G8	2-Me-pyrr	3-HO ₂ CCH ₂ -azet	G16	3-Me-pyrr	3-HO ₂ CCH ₂ -azet

(Table 34 Continued)

No	R ¹	R	No	R ¹	R
G17	2-Me-pyrr	HO ₂ C(CH ₂) ₃ NH-	G60	3-Me-pyrr	HO ₂ C(CH ₂) ₃ NH-
G18	2-Me-pyrr	HO ₂ C(CH ₂) ₂ NH-	G61	3-Me-pyrr	HO ₂ C(CH ₂) ₂ NH-
G19	2-Me-pyrr	HO ₂ CCH ₂ NH-	G62	3-Me-pyrr	HO ₂ CCH ₂ NH-
G20	2-Me-pyrr	HO ₂ C(CH ₂) ₃ N(Me)-	G63	3-Me-pyrr	HO ₂ C(CH ₂) ₃ N(Me)-
G21	2-Me-pyrr	HO ₂ C(CH ₂) ₂ N(Me)-	G64	3-Me-pyrr	HO ₂ C(CH ₂) ₂ N(Me)-
G22	2-Me-pyrr	HO ₂ CCH ₂ N(Me)-	G65	3-Me-pyrr	HO ₂ CCH ₂ N(Me)-
G23	2-Me-pyrr	HO ₂ C(CH ₂) ₃ O-	G66	3-Me-pyrr	HO ₂ C(CH ₂) ₃ O-
G24	2-Me-pyrr	HO ₂ C(CH ₂) ₂ O-	G67	3-Me-pyrr	HO ₂ C(CH ₂) ₂ O-
G25	2-Me-pyrr	HO ₂ CCH ₂ O-	G68	3-Me-pyrr	HO ₂ CCH ₂ O-
G26	iBuN(Me)-	4-HO ₂ C-pipe	G69	cBuN(Me)-	4-HO ₂ C-pipe
G27	iBuN(Me)-	3-HO ₂ C-pipe	G70	cBuN(Me)-	3-HO ₂ C-pipe
G28	iBuN(Me)-	3-HO ₂ C-pyrr	G71	cBuN(Me)-	3-HO ₂ C-pyrr
G29	iBuN(Me)-	3-HO ₂ C-azet	G72	cBuN(Me)-	3-HO ₂ C-azet
G30	iBuN(Me)-	4-HO ₂ CCH ₂ -pipe	G73	cBuN(Me)-	4-HO ₂ CCH ₂ -pipe
G31	iBuN(Me)-	4-HO ₂ CCH ₂ -pipa	G74	cBuN(Me)-	4-HO ₂ CCH ₂ -pipa
G32	iBuN(Me)-	3-HO ₂ CCH ₂ -pyrr	G75	cBuN(Me)-	3-HO ₂ CCH ₂ -pyrr
G33	iBuN(Me)-	3-HO ₂ CCH ₂ -azet	G76	cBuN(Me)-	3-HO ₂ CCH ₂ -azet
G34	iBuN(Me)-	HO ₂ C(CH ₂) ₃ NH-	G77	cBuN(Me)-	HO ₂ C(CH ₂) ₃ NH-
G35	iBuN(Me)-	HO ₂ C(CH ₂) ₂ NH-	G78	cBuN(Me)-	HO ₂ C(CH ₂) ₂ NH-
G36	iBuN(Me)-	HO ₂ CCH ₂ NH-	G79	cBuN(Me)-	HO ₂ CCH ₂ NH-
G37	iBuN(Me)-	HO ₂ C(CH ₂) ₃ N(Me)-	G80	cBuN(Me)-	HO ₂ C(CH ₂) ₃ N(Me)-
G38	iBuN(Me)-	HO ₂ C(CH ₂) ₂ N(Me)-	G81	cBuN(Me)-	HO ₂ C(CH ₂) ₂ N(Me)-
G39	iBuN(Me)-	HO ₂ CCH ₂ N(Me)-	G82	cBuN(Me)-	HO ₂ CCH ₂ N(Me)-
G40	iBuN(Me)-	HO ₂ C(CH ₂) ₃ O-	G83	cBuN(Me)-	HO ₂ C(CH ₂) ₃ O-
G41	iBuN(Me)-	HO ₂ C(CH ₂) ₂ O-	G84	cBuN(Me)-	HO ₂ C(CH ₂) ₂ O-
G42	iBuN(Me)-	HO ₂ CCH ₂ O-	G85	cBuN(Me)-	HO ₂ CCH ₂ O-
G43	iPrN(Me)-	4-HO ₂ C-pipe	G86	Me ₂ N-	4-HO ₂ C-pipe
G44	iPrN(Me)-	3-HO ₂ C-pipe	G87	Me ₂ N-	3-HO ₂ C-pipe
G45	iPrN(Me)-	3-HO ₂ C-pyrr	G88	Me ₂ N-	3-HO ₂ C-pyrr
G46	iPrN(Me)-	3-HO ₂ C-azet	G89	Me ₂ N-	3-HO ₂ C-azet
G47	iPrN(Me)-	4-HO ₂ CCH ₂ -pipe	G90	Me ₂ N-	4-HO ₂ CCH ₂ -pipe
G48	iPrN(Me)-	4-HO ₂ CCH ₂ -pipa	G91	Me ₂ N-	4-HO ₂ CCH ₂ -pipa
G49	iPrN(Me)-	3-HO ₂ CCH ₂ -pyrr	G92	Me ₂ N-	3-HO ₂ CCH ₂ -pyrr
G50	iPrN(Me)-	3-HO ₂ CCH ₂ -azet	G93	Me ₂ N-	3-HO ₂ CCH ₂ -azet
G51	iPrN(Me)-	HO ₂ C(CH ₂) ₃ NH-	G94	Me ₂ N-	HO ₂ C(CH ₂) ₃ NH-
G52	iPrN(Me)-	HO ₂ C(CH ₂) ₂ NH-	G95	Me ₂ N-	HO ₂ C(CH ₂) ₂ NH-
G53	iPrN(Me)-	HO ₂ CCH ₂ NH-	G96	Me ₂ N-	HO ₂ CCH ₂ NH-
G54	iPrN(Me)-	HO ₂ C(CH ₂) ₃ N(Me)-	G97	Me ₂ N-	HO ₂ C(CH ₂) ₃ N(Me)-
G55	iPrN(Me)-	HO ₂ C(CH ₂) ₂ N(Me)-	G98	Me ₂ N-	HO ₂ C(CH ₂) ₂ N(Me)-
G56	iPrN(Me)-	HO ₂ CCH ₂ N(Me)-	G99	Me ₂ N-	HO ₂ CCH ₂ N(Me)-
G57	iPrN(Me)-	HO ₂ C(CH ₂) ₃ O-	G100	Me ₂ N-	HO ₂ C(CH ₂) ₃ O-
G58	iPrN(Me)-	HO ₂ C(CH ₂) ₂ O-	G101	Me ₂ N-	HO ₂ C(CH ₂) ₂ O-
G59	iPrN(Me)-	HO ₂ CCH ₂ O-	G102	Me ₂ N-	HO ₂ CCH ₂ O-

(Table 35)

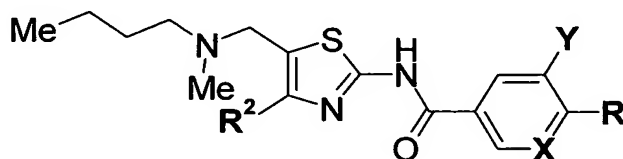


No	R ¹	R	No	R ¹	R
H1	2-Me-pyrr	4-HO ₂ C-pipe	H40	3-Me-pyrr	4-HO ₂ C-pipe
H2	2-Me-pyrr	3-HO ₂ C-pipe	H41	3-Me-pyrr	3-HO ₂ C-pipe
H3	2-Me-pyrr	3-HO ₂ C-pyrr	H42	3-Me-pyrr	3-HO ₂ C-pyrr
H4	2-Me-pyrr	3-HO ₂ C-azet	H43	3-Me-pyrr	3-HO ₂ C-azet
H5	2-Me-pyrr	4-HO ₂ CCH ₂ -pipe	H44	3-Me-pyrr	4-HO ₂ CCH ₂ -pipe
H6	2-Me-pyrr	4-HO ₂ CCH ₂ -pipa	H45	3-Me-pyrr	4-HO ₂ CCH ₂ -pipa
H7	2-Me-pyrr	3-HO ₂ CCH ₂ -pyrr	H46	3-Me-pyrr	3-HO ₂ CCH ₂ -pyrr
H8	2-Me-pyrr	3-HO ₂ CCH ₂ -azet	H47	3-Me-pyrr	3-HO ₂ CCH ₂ -azet
H9	2-Me-pyrr	HO ₂ C(CH ₂) ₃ NH-	H48	3-Me-pyrr	HO ₂ C(CH ₂) ₃ NH-
H10	2-Me-pyrr	HO ₂ C(CH ₂) ₂ NH-	H49	3-Me-pyrr	HO ₂ C(CH ₂) ₂ NH-
H11	2-Me-pyrr	HO ₂ CCH ₂ NH-	H50	3-Me-pyrr	HO ₂ CCH ₂ NH-
H12	2-Me-pyrr	HO ₂ C(CH ₂) ₃ N(Me)-	H51	3-Me-pyrr	HO ₂ C(CH ₂) ₃ N(Me)-
H13	2-Me-pyrr	HO ₂ C(CH ₂) ₂ N(Me)-	H52	3-Me-pyrr	HO ₂ C(CH ₂) ₂ N(Me)-
H14	2-Me-pyrr	HO ₂ CCH ₂ N(Me)-	H53	3-Me-pyrr	HO ₂ CCH ₂ N(Me)-
H15	2-Me-pyrr	HO ₂ C(CH ₂) ₃ O-	H54	3-Me-pyrr	HO ₂ C(CH ₂) ₃ O-
H16	2-Me-pyrr	HO ₂ C(CH ₂) ₂ O-	H55	3-Me-pyrr	HO ₂ C(CH ₂) ₂ O-
H17	2-Me-pyrr	HO ₂ CCH ₂ O-	H56	3-Me-pyrr	HO ₂ CCH ₂ O-
H18	iBuN(Me)-	4-HO ₂ C-pipe	H57	cBuN(Me)-	4-HO ₂ C-pipe
H19	iBuN(Me)-	3-HO ₂ C-pipe	H58	cBuN(Me)-	3-HO ₂ C-pipe
H20	iBuN(Me)-	3-HO ₂ C-pyrr	H59	cBuN(Me)-	3-HO ₂ C-pyrr
H21	iBuN(Me)-	3-HO ₂ C-azet	H60	cBuN(Me)-	3-HO ₂ C-azet
H22	iBuN(Me)-	4-HO ₂ CCH ₂ -pipe	H61	cBuN(Me)-	4-HO ₂ CCH ₂ -pipe
H23	iBuN(Me)-	4-HO ₂ CCH ₂ -pipa	H62	cBuN(Me)-	4-HO ₂ CCH ₂ -pipa
H24	iBuN(Me)-	3-HO ₂ CCH ₂ -pyrr	H63	cBuN(Me)-	3-HO ₂ CCH ₂ -pyrr
H25	iBuN(Me)-	3-HO ₂ CCH ₂ -azet	H64	cBuN(Me)-	3-HO ₂ CCH ₂ -azet
H26	iBuN(Me)-	HO ₂ C(CH ₂) ₃ NH-	H65	cBuN(Me)-	HO ₂ C(CH ₂) ₃ NH-
H27	iBuN(Me)-	HO ₂ C(CH ₂) ₂ NH-	H66	cBuN(Me)-	HO ₂ C(CH ₂) ₂ NH-
H28	iBuN(Me)-	HO ₂ CCH ₂ NH-	H67	cBuN(Me)-	HO ₂ CCH ₂ NH-
H29	iBuN(Me)-	HO ₂ C(CH ₂) ₃ N(Me)-	H68	cBuN(Me)-	HO ₂ C(CH ₂) ₃ N(Me)-
H30	iBuN(Me)-	HO ₂ C(CH ₂) ₂ N(Me)-	H69	cBuN(Me)-	HO ₂ C(CH ₂) ₂ N(Me)-
H31	iBuN(Me)-	HO ₂ CCH ₂ N(Me)-	H70	cBuN(Me)-	HO ₂ CCH ₂ N(Me)-
H32	iBuN(Me)-	HO ₂ C(CH ₂) ₃ O-	H71	cBuN(Me)-	HO ₂ C(CH ₂) ₃ O-
H33	iBuN(Me)-	HO ₂ C(CH ₂) ₂ O-	H72	cBuN(Me)-	HO ₂ C(CH ₂) ₂ O-
H34	iBuN(Me)-	HO ₂ CCH ₂ O-	H73	cBuN(Me)-	HO ₂ CCH ₂ O-
H35	iPrN(Me)-	4-HO ₂ C-pipe	H74	Me ₂ N-	4-HO ₂ C-pipe
H36	iPrN(Me)-	3-HO ₂ C-pipe	H75	Me ₂ N-	3-HO ₂ C-pipe
H37	iPrN(Me)-	3-HO ₂ C-pyrr	H76	Me ₂ N-	3-HO ₂ C-pyrr
H38	iPrN(Me)-	3-HO ₂ C-azet	H77	Me ₂ N-	3-HO ₂ C-azet
H39	iPrN(Me)-	4-HO ₂ CCH ₂ -pipe	H78	Me ₂ N-	4-HO ₂ CCH ₂ -pipe

(Table 35)

No	R ¹	R	No	R ¹	R
H79	iPrN(Me)-	4-HO ₂ CCH ₂ -pipa	H91	Me ₂ N-	4-HO ₂ CCH ₂ -pipa
H80	iPrN(Me)-	3-HO ₂ CCH ₂ -pyrr	H92	Me ₂ N-	3-HO ₂ CCH ₂ -pyrr
H81	iPrN(Me)-	3-HO ₂ CCH ₂ -azet	H93	Me ₂ N-	3-HO ₂ CCH ₂ -azet
H82	iPrN(Me)-	HO ₂ C(CH ₂) ₃ NH-	H94	Me ₂ N-	HO ₂ C(CH ₂) ₃ NH-
H83	iPrN(Me)-	HO ₂ C(CH ₂) ₂ NH-	H95	Me ₂ N-	HO ₂ C(CH ₂) ₂ NH-
H84	iPrN(Me)-	HO ₂ CCH ₂ NH-	H96	Me ₂ N-	HO ₂ CCH ₂ NH-
H85	iPrN(Me)-	HO ₂ C(CH ₂) ₃ N(Me)-	H97	Me ₂ N-	HO ₂ C(CH ₂) ₃ N(Me)-
H86	iPrN(Me)-	HO ₂ C(CH ₂) ₂ N(Me)-	H98	Me ₂ N-	HO ₂ C(CH ₂) ₂ N(Me)-
H87	iPrN(Me)-	HO ₂ CCH ₂ N(Me)-	H99	Me ₂ N-	HO ₂ CCH ₂ N(Me)-
H88	iPrN(Me)-	HO ₂ C(CH ₂) ₃ O-	H100	Me ₂ N-	HO ₂ C(CH ₂) ₃ O-
H89	iPrN(Me)-	HO ₂ C(CH ₂) ₂ O-	H101	Me ₂ N-	HO ₂ C(CH ₂) ₂ O-
H90	iPrN(Me)-	HO ₂ CCH ₂ O-	H102	Me ₂ N-	HO ₂ CCH ₂ O-

(Table 36)



No	R ²	X	Y	R
11	4-Cl-2-The	N	Cl	4-HO(CH ₂) ₂ -pipe
12	4-Cl-2-The	N	Cl	4-MeO-pipe
13	4-Cl-2-The	N	Cl	MeO(CH ₂) ₃ O-
14	4-Cl-2-The	N	Cl	MeO(CH ₂) ₂ O-
15	4-Cl-2-The	N	Cl	H ₂ O ₃ P-(CH ₂) ₃ NH-
16	4-Cl-2-The	N	Cl	4-H ₂ O ₃ P-pipe
17	4-Cl-2-The	N	Cl	(EtO) ₂ (O)P-(CH ₂) ₃ NH-
18	4-Cl-2-The	N	Cl	4-(EtO) ₂ (O)P-pipe
19	4-Cl-2-The	N	Cl	4-NC-pipe
110	4-Cl-2-The	N	Cl	3-oxo-pipa
111	4-Cl-2-The	C-H	Cl	4-HO-pipe
112	4-Cl-2-The	C-H	Cl	4-HOCH ₂ -pipe
113	4-Cl-2-The	C-H	Cl	4-HO(CH ₂) ₂ -pipe
114	4-Cl-2-The	C-H	Cl	4-MeO-pipe
115	4-Cl-2-The	C-H	Cl	MeO(CH ₂) ₃ O-
116	4-Cl-2-The	C-H	Cl	MeO(CH ₂) ₂ O-
117	4-Cl-2-The	C-H	Cl	H ₂ O ₃ P-(CH ₂) ₃ NH-
118	4-Cl-2-The	C-H	Cl	4-H ₂ O ₃ P-pipe
119	4-Cl-2-The	C-H	Cl	(EtO) ₂ (O)P-(CH ₂) ₃ NH-
120	4-Cl-2-The	C-H	Cl	4-(EtO) ₂ (O)P-pipe
121	4-Cl-2-The	C-H	Cl	4-NC-pipe
122	4-Cl-2-The	C-H	Cl	3-oxo-pipa
123	4-Cl-2-The	C-F	F	4-HO-pipe

(Table 36 Continued)

No	R ²	X	Y	R
124	4-Cl-2-The	C-F	F	4-HOCH ₂ -pipe
125	4-Cl-2-The	C-F	F	4-HO(CH ₂) ₂ -pipe
126	4-Cl-2-The	C-F	F	4-MeO-pipe
127	4-Cl-2-The	C-F	F	MeO(CH ₂) ₃ O-
128	4-Cl-2-The	C-F	F	MeO(CH ₂) ₂ O-
129	4-Cl-2-The	C-F	F	H ₂ O ₃ P-(CH ₂) ₃ NH-
130	4-Cl-2-The	C-F	F	4-H ₂ O ₃ P-pipe
131	4-Cl-2-The	C-F	F	(EtO) ₂ (O)P-(CH ₂) ₃ NH-
132	4-Cl-2-The	C-F	F	4-(EtO) ₂ (O)P-pipe
133	4-Cl-2-The	C-F	F	4-NC-pipe
134	4-Cl-2-The	C-F	F	3-oxo-pipa
135	4-Me-2-The	N	Cl	HO(CH ₂) ₃ NH-
136	4-Me-2-The	N	Cl	HO(CH ₂) ₃ N(Me)-
137	4-Me-2-The	N	Cl	HO(CH ₂) ₃ O-
138	4-Me-2-The	N	Cl	HO(CH ₂) ₂ O-
139	4-Me-2-The	N	Cl	4-HO-pipe
140	4-Me-2-The	N	Cl	4-HOCH ₂ -pipe
141	4-Me-2-The	N	Cl	4-HO(CH ₂) ₂ -pipe
142	4-Me-2-The	N	Cl	4-MeO-pipe
143	4-Me-2-The	N	Cl	MeO(CH ₂) ₃ O-
144	4-Me-2-The	N	Cl	MeO(CH ₂) ₂ O-
145	4-Me-2-The	N	Cl	H ₂ O ₃ P-(CH ₂) ₃ NH-
146	4-Me-2-The	N	Cl	4-H ₂ O ₃ P-pipe
147	4-Me-2-The	N	Cl	(EtO) ₂ (O)P-(CH ₂) ₃ NH-
148	4-Me-2-The	N	Cl	4-(EtO) ₂ (O)P-pipe
149	4-Me-2-The	N	Cl	4-NC-pipe
150	4-Me-2-The	N	Cl	3-oxo-pipa
151	4-Me-2-The	C-H	Cl	HO(CH ₂) ₃ NH-
152	4-Me-2-The	C-H	Cl	HO(CH ₂) ₃ N(Me)-
153	4-Me-2-The	C-H	Cl	HO(CH ₂) ₃ O-
154	4-Me-2-The	C-H	Cl	HO(CH ₂) ₂ O-
155	4-Me-2-The	C-H	Cl	4-HO-pipe
156	4-Me-2-The	C-H	Cl	4-HOCH ₂ -pipe
157	4-Me-2-The	C-H	Cl	4-HO(CH ₂) ₂ -pipe
158	4-Me-2-The	C-H	Cl	4-MeO-pipe
159	4-Me-2-The	C-H	Cl	MeO(CH ₂) ₃ O-
160	4-Me-2-The	C-H	Cl	MeO(CH ₂) ₂ O-
161	4-Me-2-The	C-H	Cl	H ₂ O ₃ P-(CH ₂) ₃ NH-
162	4-Me-2-The	C-H	Cl	4-H ₂ O ₃ P-pipe
163	4-Me-2-The	C-H	Cl	(EtO) ₂ (O)P-(CH ₂) ₃ NH-
164	4-Me-2-The	C-H	Cl	4-(EtO) ₂ (O)P-pipe
165	4-Me-2-The	C-H	Cl	4-NC-pipe
166	4-Me-2-The	C-H	Cl	3-oxo-pipa
167	4-Me-2-The	C-F	F	HO(CH ₂) ₃ NH-

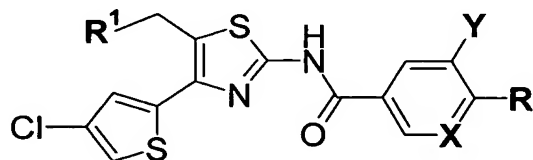
(Table 36 Continued)

No	R ²	X	Y	R
168	4-Me-2-The	C-F	F	HO(CH ₂) ₃ N(Me)-
169	4-Me-2-The	C-F	F	HO(CH ₂) ₃ O-
170	4-Me-2-The	C-F	F	HO(CH ₂) ₂ O-
171	4-Me-2-The	C-F	F	4-HO-pipe
172	4-Me-2-The	C-F	F	4-HOCH ₂ -pipe
173	4-Me-2-The	C-F	F	4-HO(CH ₂) ₂ -pipe
174	4-Me-2-The	C-F	F	4-MeO-pipe
175	4-Me-2-The	C-F	F	MeO(CH ₂) ₃ O-
176	4-Me-2-The	C-F	F	MeO(CH ₂) ₂ O-
177	4-Me-2-The	C-F	F	H ₂ O ₃ P-(CH ₂) ₃ NH-
178	4-Me-2-The	C-F	F	4-H ₂ O ₃ P-pipe
179	4-Me-2-The	C-F	F	(EtO) ₂ (O)P-(CH ₂) ₃ NH-
180	4-Me-2-The	C-F	F	4-(EtO) ₂ (O)P-pipe
181	4-Me-2-The	C-F	F	4-NC-pipe
182	4-Me-2-The	C-F	F	3-oxo-pipa
183	3-F ₃ C-Ph	N	Cl	HO(CH ₂) ₃ NH-
184	3-F ₃ C-Ph	N	Cl	HO(CH ₂) ₃ N(Me)-
185	3-F ₃ C-Ph	N	Cl	HO(CH ₂) ₃ O-
186	3-F ₃ C-Ph	N	Cl	HO(CH ₂) ₂ O-
187	3-F ₃ C-Ph	N	Cl	4-HO-pipe
188	3-F ₃ C-Ph	N	Cl	4-HOCH ₂ -pipe
189	3-F ₃ C-Ph	N	Cl	4-HO(CH ₂) ₂ -pipe
190	3-F ₃ C-Ph	N	Cl	4-MeO-pipe
191	3-F ₃ C-Ph	N	Cl	MeO(CH ₂) ₃ O-
192	3-F ₃ C-Ph	N	Cl	MeO(CH ₂) ₂ O-
193	3-F ₃ C-Ph	N	Cl	H ₂ O ₃ P-(CH ₂) ₃ NH-
194	3-F ₃ C-Ph	N	Cl	4-H ₂ O ₃ P-pipe
195	3-F ₃ C-Ph	N	Cl	(EtO) ₂ (O)P-(CH ₂) ₃ NH-
196	3-F ₃ C-Ph	N	Cl	4-(EtO) ₂ (O)P-pipe
197	3-F ₃ C-Ph	N	Cl	4-NC-pipe
198	3-F ₃ C-Ph	N	Cl	3-oxo-pipa
199	3-F ₃ C-Ph	C-H	Cl	HO(CH ₂) ₃ NH-
1100	3-F ₃ C-Ph	C-H	Cl	HO(CH ₂) ₃ N(Me)-
1101	3-F ₃ C-Ph	C-H	Cl	HO(CH ₂) ₃ O-
1102	3-F ₃ C-Ph	C-H	Cl	HO(CH ₂) ₂ O-
1103	3-F ₃ C-Ph	C-H	Cl	4-HO-pipe
1104	3-F ₃ C-Ph	C-H	Cl	4-HOCH ₂ -pipe
1105	3-F ₃ C-Ph	C-H	Cl	4-HO(CH ₂) ₂ -pipe
1106	3-F ₃ C-Ph	C-H	Cl	4-MeO-pipe
1107	3-F ₃ C-Ph	C-H	Cl	MeO(CH ₂) ₃ O-
1108	3-F ₃ C-Ph	C-H	Cl	MeO(CH ₂) ₂ O-
1109	3-F ₃ C-Ph	C-H	Cl	H ₂ O ₃ P-(CH ₂) ₃ NH-
1110	3-F ₃ C-Ph	C-H	Cl	4-H ₂ O ₃ P-pipe
1111	3-F ₃ C-Ph	C-H	Cl	(EtO) ₂ (O)P-(CH ₂) ₃ NH-

(Table 36 Continued)

No	R ²	X	Y	R
I112	3-F ₃ C-Ph	C-H	Cl	4-(EtO) ₂ (O)P-pipe
I113	3-F ₃ C-Ph	C-H	Cl	4-NC-pipe
I114	3-F ₃ C-Ph	C-H	Cl	3-oxo-pipa
I115	3-F ₃ C-Ph	C-F	F	HO(CH ₂) ₃ NH-
I116	3-F ₃ C-Ph	C-F	F	HO(CH ₂) ₃ N(Me)-
I117	3-F ₃ C-Ph	C-F	F	HO(CH ₂) ₃ O-
I118	3-F ₃ C-Ph	C-F	F	HO(CH ₂) ₂ O-
I119	3-F ₃ C-Ph	C-F	F	4-HO-pipe
I120	3-F ₃ C-Ph	C-F	F	4-HOCH ₂ -pipe
I121	3-F ₃ C-Ph	C-F	F	4-HO(CH ₂) ₂ -pipe
I122	3-F ₃ C-Ph	C-F	F	4-MeO-pipe
I123	3-F ₃ C-Ph	C-F	F	MeO(CH ₂) ₃ O-
I124	3-F ₃ C-Ph	C-F	F	MeO(CH ₂) ₂ O-
I125	3-F ₃ C-Ph	C-F	F	H ₂ O ₃ P-(CH ₂) ₃ NH-
I126	3-F ₃ C-Ph	C-F	F	4-H ₂ O ₃ P-pipe
I127	3-F ₃ C-Ph	C-F	F	(EtO) ₂ (O)P-(CH ₂) ₃ NH-
I128	3-F ₃ C-Ph	C-F	F	4-(EtO) ₂ (O)P-pipe
I129	3-F ₃ C-Ph	C-F	F	4-NC-pipe
I130	3-F ₃ C-Ph	C-F	F	3-oxo-pipa

(Table 37)



No	R ¹	X	Y	R
J1	cBuN(Me)-	N	Cl	HO(CH ₂) ₃ NH-
J2	cBuN(Me)-	N	Cl	HO(CH ₂) ₃ N(Me)-
J3	cBuN(Me)-	N	Cl	HO(CH ₂) ₃ O-
J4	cBuN(Me)-	N	Cl	HO(CH ₂) ₂ O-
J5	cBuN(Me)-	N	Cl	4-HO-pipe
J6	cBuN(Me)-	N	Cl	4-HOCH ₂ -pipe
J7	cBuN(Me)-	N	Cl	4-HO(CH ₂) ₂ -pipe
J8	cBuN(Me)-	N	Cl	4-MeO-pipe
J9	cBuN(Me)-	N	Cl	MeO(CH ₂) ₃ O-
J10	cBuN(Me)-	N	Cl	MeO(CH ₂) ₂ O-
J11	cBuN(Me)-	N	Cl	H ₂ O ₃ P-(CH ₂) ₃ NH-
J12	cBuN(Me)-	N	Cl	4-H ₂ O ₃ P-pipe
J13	cBuN(Me)-	N	Cl	(EtO) ₂ (O)P-(CH ₂) ₃ NH-
J14	cBuN(Me)-	N	Cl	4-(EtO) ₂ (O)P-pipe
J15	cBuN(Me)-	N	Cl	4-NC-pipe
J16	cBuN(Me)-	N	Cl	3-oxo-pipa

(Table 37 Continued)

No	R ¹	X	Y	R
J17	cBuN(Me)-	C-H	Cl	HO(CH ₂) ₃ NH-
J18	cBuN(Me)-	C-H	Cl	HO(CH ₂) ₃ N(Me)-
J19	cBuN(Me)-	C-H	Cl	HO(CH ₂) ₃ O-
J20	cBuN(Me)-	C-H	Cl	HO(CH ₂) ₂ O-
J21	cBuN(Me)-	C-H	Cl	4-HO-pipe
J22	cBuN(Me)-	C-H	Cl	4-HOCH ₂ -pipe
J23	cBuN(Me)-	C-H	Cl	4-HO(CH ₂) ₂ -pipe
J24	cBuN(Me)-	C-H	Cl	4-MeO-pipe
J25	cBuN(Me)-	C-H	Cl	MeO(CH ₂) ₃ O-
J26	cBuN(Me)-	C-H	Cl	MeO(CH ₂) ₂ O-
J27	cBuN(Me)-	C-H	Cl	H ₂ O ₃ P-(CH ₂) ₃ NH-
J28	cBuN(Me)-	C-H	Cl	4-H ₂ O ₃ P-pipe
J29	cBuN(Me)-	C-H	Cl	(EtO) ₂ (O)P-(CH ₂) ₃ NH-
J30	cBuN(Me)-	C-H	Cl	4-(EtO) ₂ (O)P-pipe
J31	cBuN(Me)-	C-H	Cl	4-NC-pipe
J32	cBuN(Me)-	C-H	Cl	3-oxo-pipa
J33	iBuN(Me)-	N	Cl	HO(CH ₂) ₃ NH-
J34	iBuN(Me)-	N	Cl	HO(CH ₂) ₃ N(Me)-
J35	iBuN(Me)-	N	Cl	HO(CH ₂) ₃ O-
J36	iBuN(Me)-	N	Cl	HO(CH ₂) ₂ O-
J37	iBuN(Me)-	N	Cl	4-HO-pipe
J38	iBuN(Me)-	N	Cl	4-HOCH ₂ -pipe
J39	iBuN(Me)-	N	Cl	4-HO(CH ₂) ₂ -pipe
J40	iBuN(Me)-	N	Cl	4-MeO-pipe
J41	iBuN(Me)-	N	Cl	MeO(CH ₂) ₃ O-
J42	iBuN(Me)-	N	Cl	MeO(CH ₂) ₂ O-
J43	iBuN(Me)-	N	Cl	H ₂ O ₃ P-(CH ₂) ₃ NH-
J44	iBuN(Me)-	N	Cl	4-H ₂ O ₃ P-pipe
J45	iBuN(Me)-	N	Cl	(EtO) ₂ (O)P-(CH ₂) ₃ NH-
J46	iBuN(Me)-	N	Cl	4-(EtO) ₂ (O)P-pipe
J47	iBuN(Me)-	N	Cl	4-NC-pipe
J48	iBuN(Me)-	N	Cl	3-oxo-pipa
J49	iBuN(Me)-	C-H	Cl	HO(CH ₂) ₃ NH-
J50	iBuN(Me)-	C-H	Cl	HO(CH ₂) ₃ N(Me)-
J51	iBuN(Me)-	C-H	Cl	HO(CH ₂) ₃ O-
J52	iBuN(Me)-	C-H	Cl	HO(CH ₂) ₂ O-
J53	iBuN(Me)-	C-H	Cl	4-HO-pipe
J54	iBuN(Me)-	C-H	Cl	4-HOCH ₂ -pipe
J55	iBuN(Me)-	C-H	Cl	4-HO(CH ₂) ₂ -pipe
J56	iBuN(Me)-	C-H	Cl	4-MeO-pipe
J57	iBuN(Me)-	C-H	Cl	MeO(CH ₂) ₃ O-
J58	iBuN(Me)-	C-H	Cl	MeO(CH ₂) ₂ O-
J59	iBuN(Me)-	C-H	Cl	H ₂ O ₃ P-(CH ₂) ₃ NH-
J60	iBuN(Me)-	C-H	Cl	4-H ₂ O ₃ P-pipe

(Table 37 Continued)

No	R ¹	X	Y	R
J61	iBuN(Me)-	C-H	Cl	(EtO) ₂ (O)P-(CH ₂) ₃ NH-
J62	iBuN(Me)-	C-H	Cl	4-(EtO) ₂ (O)P-pipe
J63	iBuN(Me)-	C-H	Cl	4-NC-pipe
J64	iBuN(Me)-	C-H	Cl	3-oxo-pipa
J65	pipe	N	Cl	HO(CH ₂) ₃ NH-
J66	pipe	N	Cl	HO(CH ₂) ₃ N(Me)-
J67	pipe	N	Cl	HO(CH ₂) ₃ O-
J68	pipe	N	Cl	HO(CH ₂) ₂ O-
J69	pipe	N	Cl	4-HO-pipe
J70	pipe	N	Cl	4-HOCH ₂ -pipe
J71	pipe	N	Cl	4-HO(CH ₂) ₂ -pipe
J72	pipe	N	Cl	4-MeO-pipe
J73	pipe	N	Cl	MeO(CH ₂) ₃ O-
J74	pipe	N	Cl	MeO(CH ₂) ₂ O-
J75	pipe	N	Cl	H ₂ O ₃ P-(CH ₂) ₃ NH-
J76	pipe	N	Cl	4-H ₂ O ₃ P-pipe
J77	pipe	N	Cl	(EtO) ₂ (O)P-(CH ₂) ₃ NH-
J78	pipe	N	Cl	4-(EtO) ₂ (O)P-pipe
J79	pipe	N	Cl	4-NC-pipe
J80	pipe	N	Cl	3-oxo-pipa
J81	pipe	C-H	Cl	HO(CH ₂) ₃ NH-
J82	pipe	C-H	Cl	HO(CH ₂) ₃ N(Me)-
J83	pipe	C-H	Cl	HO(CH ₂) ₃ O-
J84	pipe	C-H	Cl	HO(CH ₂) ₂ O-
J85	pipe	C-H	Cl	4-HO-pipe
J86	pipe	C-H	Cl	4-HOCH ₂ -pipe
J87	pipe	C-H	Cl	4-HO(CH ₂) ₂ -pipe
J88	pipe	C-H	Cl	4-MeO-pipe
J89	pipe	C-H	Cl	MeO(CH ₂) ₃ O-
J90	pipe	C-H	Cl	MeO(CH ₂) ₂ O-
J91	pipe	C-H	Cl	H ₂ O ₃ P-(CH ₂) ₃ NH-
J92	pipe	C-H	Cl	4-H ₂ O ₃ P-pipe
J93	pipe	C-H	Cl	(EtO) ₂ (O)P-(CH ₂) ₃ NH-
J94	pipe	C-H	Cl	4-(EtO) ₂ (O)P-pipe
J95	pipe	C-H	Cl	4-NC-pipe
J96	pipe	C-H	Cl	3-oxo-pipa
J97	2-Me-pyrr	N	Cl	HO(CH ₂) ₃ NH-
J98	2-Me-pyrr	N	Cl	HO(CH ₂) ₃ N(Me)-
J99	2-Me-pyrr	N	Cl	HO(CH ₂) ₃ O-
J100	2-Me-pyrr	N	Cl	HO(CH ₂) ₂ O-
J101	2-Me-pyrr	N	Cl	4-HO-pipe
J102	2-Me-pyrr	N	Cl	4-HOCH ₂ -pipe
J103	2-Me-pyrr	N	Cl	4-HO(CH ₂) ₂ -pipe
J104	2-Me-pyrr	N	Cl	4-MeO-pipe

(Table 37 Continued)

No	R ¹	X	Y	R
J105	2-Me-pyrr	N	Cl	MeO(CH ₂) ₃ O-
J106	2-Me-pyrr	N	Cl	MeO(CH ₂) ₂ O-
J107	2-Me-pyrr	N	Cl	H ₂ O ₃ P-(CH ₂) ₃ NH-
J108	2-Me-pyrr	N	Cl	4-H ₂ O ₃ P-pipe
J109	2-Me-pyrr	N	Cl	(EtO) ₂ (O)P-(CH ₂) ₃ NH-
J110	2-Me-pyrr	N	Cl	4-(EtO) ₂ (O)P-pipe
J111	2-Me-pyrr	N	Cl	4-NC-pipe
J112	2-Me-pyrr	N	Cl	3-oxo-pipa
J113	2-Me-pyrr	C-H	Cl	HO(CH ₂) ₃ NH-
J114	2-Me-pyrr	C-H	Cl	HO(CH ₂) ₃ N(Me)-
J115	2-Me-pyrr	C-H	Cl	HO(CH ₂) ₃ O-
J116	2-Me-pyrr	C-H	Cl	HO(CH ₂) ₂ O-
J117	2-Me-pyrr	C-H	Cl	4-HO-pipe
J118	2-Me-pyrr	C-H	Cl	4-HOCH ₂ -pipe
J119	2-Me-pyrr	C-H	Cl	4-HO(CH ₂) ₂ -pipe
J120	2-Me-pyrr	C-H	Cl	4-MeO-pipe
J121	2-Me-pyrr	C-H	Cl	MeO(CH ₂) ₃ O-
J122	2-Me-pyrr	C-H	Cl	MeO(CH ₂) ₂ O-
J123	2-Me-pyrr	C-H	Cl	H ₂ O ₃ P-(CH ₂) ₃ NH-
J124	2-Me-pyrr	C-H	Cl	4-H ₂ O ₃ P-pipe
J125	2-Me-pyrr	C-H	Cl	(EtO) ₂ (O)P-(CH ₂) ₃ NH-
J126	2-Me-pyrr	C-H	Cl	4-(EtO) ₂ (O)P-pipe
J127	2-Me-pyrr	C-H	Cl	4-NC-pipe
J128	2-Me-pyrr	C-H	Cl	3-oxo-pipa
J129	3-Me-pyrr	N	Cl	HO(CH ₂) ₃ NH-
J130	3-Me-pyrr	N	Cl	HO(CH ₂) ₃ N(Me)-
J131	3-Me-pyrr	N	Cl	HO(CH ₂) ₃ O-
J132	3-Me-pyrr	N	Cl	HO(CH ₂) ₂ O-
J133	3-Me-pyrr	N	Cl	4-HO-pipe
J134	3-Me-pyrr	N	Cl	4-HOCH ₂ -pipe
J135	3-Me-pyrr	N	Cl	4-HO(CH ₂) ₂ -pipe
J136	3-Me-pyrr	N	Cl	4-MeO-pipe
J137	3-Me-pyrr	N	Cl	MeO(CH ₂) ₃ O-
J138	3-Me-pyrr	N	Cl	MeO(CH ₂) ₂ O-
J139	3-Me-pyrr	N	Cl	H ₂ O ₃ P-(CH ₂) ₃ NH-
J140	3-Me-pyrr	N	Cl	4-H ₂ O ₃ P-pipe
J141	3-Me-pyrr	N	Cl	(EtO) ₂ (O)P-(CH ₂) ₃ NH-
J142	3-Me-pyrr	N	Cl	4-(EtO) ₂ (O)P-pipe
J143	3-Me-pyrr	N	Cl	4-NC-pipe
J144	3-Me-pyrr	N	Cl	3-oxo-pipa
J145	3-Me-pyrr	C-H	Cl	HO(CH ₂) ₃ NH-
J146	3-Me-pyrr	C-H	Cl	HO(CH ₂) ₃ N(Me)-
J147	3-Me-pyrr	C-H	Cl	HO(CH ₂) ₃ O-
J148	3-Me-pyrr	C-H	Cl	HO(CH ₂) ₂ O-

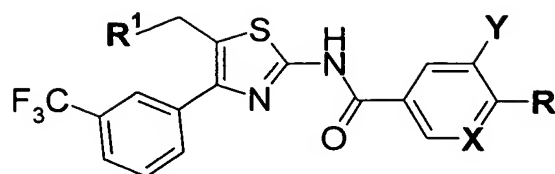
(Table 37 Continued)

No	R ¹	X	Y	R
J149	3-Me-pyrr	C-H	Cl	4-HO-pipe
J150	3-Me-pyrr	C-H	Cl	4-HOCH ₂ -pipe
J151	3-Me-pyrr	C-H	Cl	4-HO(CH ₂) ₂ -pipe
J152	3-Me-pyrr	C-H	Cl	4-MeO-pipe
J153	3-Me-pyrr	C-H	Cl	MeO(CH ₂) ₃ O-
J154	3-Me-pyrr	C-H	Cl	MeO(CH ₂) ₂ O-
J155	3-Me-pyrr	C-H	Cl	H ₂ O ₃ P-(CH ₂) ₃ NH-
J156	3-Me-pyrr	C-H	Cl	4-H ₂ O ₃ P-pipe
J157	3-Me-pyrr	C-H	Cl	(EtO) ₂ (O)P-(CH ₂) ₃ NH-
J158	3-Me-pyrr	C-H	Cl	4-(EtO) ₂ (O)P-pipe
J159	3-Me-pyrr	C-H	Cl	4-NC-pipe
J160	3-Me-pyrr	C-H	Cl	3-oxo-pipa
J161	iPrN(Me)-	N	Cl	HO(CH ₂) ₃ NH-
J162	iPrN(Me)-	N	Cl	HO(CH ₂) ₃ N(Me)-
J163	iPrN(Me)-	N	Cl	HO(CH ₂) ₃ O-
J164	iPrN(Me)-	N	Cl	HO(CH ₂) ₂ O-
J165	iPrN(Me)-	N	Cl	4-HO-pipe
J166	iPrN(Me)-	N	Cl	4-HOCH ₂ -pipe
J167	iPrN(Me)-	N	Cl	4-HO(CH ₂) ₂ -pipe
J168	iPrN(Me)-	N	Cl	4-MeO-pipe
J169	iPrN(Me)-	N	Cl	MeO(CH ₂) ₃ O-
J170	iPrN(Me)-	N	Cl	MeO(CH ₂) ₂ O-
J171	iPrN(Me)-	N	Cl	H ₂ O ₃ P-(CH ₂) ₃ NH-
J172	iPrN(Me)-	N	Cl	4-H ₂ O ₃ P-pipe
J173	iPrN(Me)-	N	Cl	(EtO) ₂ (O)P-(CH ₂) ₃ NH-
J174	iPrN(Me)-	N	Cl	4-(EtO) ₂ (O)P-pipe
J175	iPrN(Me)-	N	Cl	4-NC-pipe
J176	iPrN(Me)-	N	Cl	3-oxo-pipa
J177	iPrN(Me)-	C-H	Cl	HO(CH ₂) ₃ NH-
J178	iPrN(Me)-	C-H	Cl	HO(CH ₂) ₃ N(Me)-
J179	iPrN(Me)-	C-H	Cl	HO(CH ₂) ₃ O-
J180	iPrN(Me)-	C-H	Cl	HO(CH ₂) ₂ O-
J181	iPrN(Me)-	C-H	Cl	4-HO-pipe
J182	iPrN(Me)-	C-H	Cl	4-HOCH ₂ -pipe
J183	iPrN(Me)-	C-H	Cl	4-HO(CH ₂) ₂ -pipe
J184	iPrN(Me)-	C-H	Cl	4-MeO-pipe
J185	iPrN(Me)-	C-H	Cl	MeO(CH ₂) ₃ O-
J186	iPrN(Me)-	C-H	Cl	MeO(CH ₂) ₂ O-
J187	iPrN(Me)-	C-H	Cl	H ₂ O ₃ P-(CH ₂) ₃ NH-
J188	iPrN(Me)-	C-H	Cl	4-H ₂ O ₃ P-pipe
J189	iPrN(Me)-	C-H	Cl	(EtO) ₂ (O)P-(CH ₂) ₃ NH-
J190	iPrN(Me)-	C-H	Cl	4-(EtO) ₂ (O)P-pipe
J191	iPrN(Me)-	C-H	Cl	4-NC-pipe
J192	iPrN(Me)-	C-H	Cl	3-oxo-pipa

(Table 37 Continued)

No	R ¹	X	Y	R
J193	Me ₂ N-	N	Cl	HO(CH ₂) ₃ NH-
J194	Me ₂ N-	N	Cl	HO(CH ₂) ₃ N(Me)-
J195	Me ₂ N-	N	Cl	HO(CH ₂) ₃ O-
J196	Me ₂ N-	N	Cl	HO(CH ₂) ₂ O-
J197	Me ₂ N-	N	Cl	4-HO-pipe
J198	Me ₂ N-	N	Cl	4-HOCH ₂ -pipe
J199	Me ₂ N-	N	Cl	4-HO(CH ₂) ₂ -pipe
J200	Me ₂ N-	N	Cl	4-MeO-pipe
J201	Me ₂ N-	N	Cl	MeO(CH ₂) ₃ O-
J202	Me ₂ N-	N	Cl	MeO(CH ₂) ₂ O-
J203	Me ₂ N-	N	Cl	H ₂ O ₃ P-(CH ₂) ₃ NH-
J204	Me ₂ N-	N	Cl	4-H ₂ O ₃ P-pipe
J205	Me ₂ N-	N	Cl	(EtO) ₂ (O)P-(CH ₂) ₃ NH-
J206	Me ₂ N-	N	Cl	4-(EtO) ₂ (O)P-pipe
J207	Me ₂ N-	N	Cl	4-NC-pipe
J208	Me ₂ N-	N	Cl	3-oxo-pipa
J209	Me ₂ N-	C-H	Cl	HO(CH ₂) ₃ NH-
J210	Me ₂ N-	C-H	Cl	HO(CH ₂) ₃ N(Me)-
J211	Me ₂ N-	C-H	Cl	HO(CH ₂) ₃ O-
J212	Me ₂ N-	C-H	Cl	HO(CH ₂) ₂ O-
J213	Me ₂ N-	C-H	Cl	4-HO-pipe
J214	Me ₂ N-	C-H	Cl	4-HOCH ₂ -pipe
J215	Me ₂ N-	C-H	Cl	4-HO(CH ₂) ₂ -pipe
J216	Me ₂ N-	C-H	Cl	4-MeO-pipe
J217	Me ₂ N-	C-H	Cl	MeO(CH ₂) ₃ O-
J218	Me ₂ N-	C-H	Cl	MeO(CH ₂) ₂ O-
J219	Me ₂ N-	C-H	Cl	H ₂ O ₃ P-(CH ₂) ₃ NH-
J220	Me ₂ N-	C-H	Cl	4-H ₂ O ₃ P-pipe
J221	Me ₂ N-	C-H	Cl	(EtO) ₂ (O)P-(CH ₂) ₃ NH-
J222	Me ₂ N-	C-H	Cl	4-(EtO) ₂ (O)P-pipe
J223	Me ₂ N-	C-H	Cl	4-NC-pipe
J224	Me ₂ N-	C-H	Cl	3-oxo-pipa

(Table 38)



No	R ¹	X	Y	R
K1	nBuN(Me)-	C-H	Cl	4-H ₂ NOC-pipe
K2	nBuN(Me)-	C-F	F	4-H ₂ NOC-pipe
K3	cBuN(Me)-	C-H	Cl	4-HO-pipe
K4	cBuN(Me)-	C-H	Cl	4-MeO-pipe
K5	cBuN(Me)-	C-H	Cl	4-H ₂ O ₃ P-pipe
K6	cBuN(Me)-	C-H	Cl	4-(EtO) ₂ (O)P-pipe
K7	cBuN(Me)-	C-H	Cl	4-NC-pipe
K8	cBuN(Me)-	C-H	Cl	4-H ₂ NOC-pipe
K9	cBuN(Me)-	C-F	F	4-HO-pipe
K10	cBuN(Me)-	C-F	F	4-MeO-pipe
K11	cBuN(Me)-	C-F	F	4-H ₂ O ₃ P-pipe
K12	cBuN(Me)-	C-F	F	4-(EtO) ₂ (O)P-pipe
K13	cBuN(Me)-	C-F	F	4-NC-pipe
K14	cBuN(Me)-	C-F	F	4-H ₂ NOC-pipe
K15	iBuN(Me)-	C-H	Cl	4-HO-pipe
K16	iBuN(Me)-	C-H	Cl	4-MeO-pipe
K17	iBuN(Me)-	C-H	Cl	4-H ₂ O ₃ P-pipe
K18	iBuN(Me)-	C-H	Cl	4-(EtO) ₂ (O)P-pipe
K19	iBuN(Me)-	C-H	Cl	4-NC-pipe
K20	iBuN(Me)-	C-H	Cl	4-H ₂ NOC-pipe
K21	iBuN(Me)-	C-F	F	4-HO-pipe
K22	iBuN(Me)-	C-F	F	4-MeO-pipe
K23	iBuN(Me)-	C-F	F	4-H ₂ O ₃ P-pipe
K24	iBuN(Me)-	C-F	F	4-(EtO) ₂ (O)P-pipe
K25	iBuN(Me)-	C-F	F	4-NC-pipe
K26	iBuN(Me)-	C-F	F	4-H ₂ NOC-pipe
K27	pipe	C-H	Cl	4-HO-pipe
K28	pipe	C-H	Cl	4-MeO-pipe
K29	pipe	C-H	Cl	4-H ₂ O ₃ P-pipe
K30	pipe	C-H	Cl	4-(EtO) ₂ (O)P-pipe
K31	pipe	C-H	Cl	4-NC-pipe
K32	pipe	C-H	Cl	4-H ₂ NOC-pipe
K33	pipe	C-F	F	4-HO-pipe
K34	pipe	C-F	F	4-MeO-pipe
K35	pipe	C-F	F	4-H ₂ O ₃ P-pipe
K36	pipe	C-F	F	4-(EtO) ₂ (O)P-pipe
K37	pipe	C-F	F	4-NC-pipe

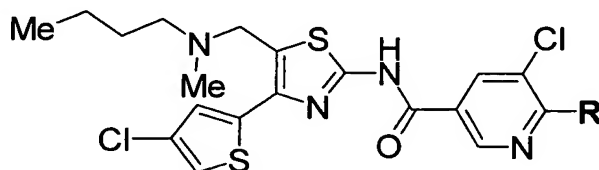
(Table 38 Continued)

No	R ¹	X	Y	R
K38	pipe	C-F	F	4-H ₂ NOC-pipe
K39	2-Me-pyrr	C-H	Cl	4-HO-pipe
K40	2-Me-pyrr	C-H	Cl	4-MeO-pipe
K41	2-Me-pyrr	C-H	Cl	4-H ₂ O ₃ P-pipe
K42	2-Me-pyrr	C-H	Cl	4-(EtO) ₂ (O)P-pipe
K43	2-Me-pyrr	C-H	Cl	4-NC-pipe
K44	2-Me-pyrr	C-H	Cl	4-H ₂ NOC-pipe
K45	2-Me-pyrr	C-F	F	4-HO-pipe
K46	2-Me-pyrr	C-F	F	4-MeO-pipe
K47	2-Me-pyrr	C-F	F	4-H ₂ O ₃ P-pipe
K48	2-Me-pyrr	C-F	F	4-(EtO) ₂ (O)P-pipe
K49	2-Me-pyrr	C-F	F	4-NC-pipe
K50	2-Me-pyrr	C-F	F	4-H ₂ NOC-pipe
K51	3-Me-pyrr	C-H	Cl	4-HO-pipe
K52	3-Me-pyrr	C-H	Cl	4-MeO-pipe
K53	3-Me-pyrr	C-H	Cl	4-H ₂ O ₃ P-pipe
K54	3-Me-pyrr	C-H	Cl	4-(EtO) ₂ (O)P-pipe
K55	3-Me-pyrr	C-H	Cl	4-NC-pipe
K56	3-Me-pyrr	C-H	Cl	4-H ₂ NOC-pipe
K57	3-Me-pyrr	C-F	F	4-HO-pipe
K58	3-Me-pyrr	C-F	F	4-MeO-pipe
K59	3-Me-pyrr	C-F	F	4-H ₂ O ₃ P-pipe
K60	3-Me-pyrr	C-F	F	4-(EtO) ₂ (O)P-pipe
K61	3-Me-pyrr	C-F	F	4-NC-pipe
K62	3-Me-pyrr	C-F	F	4-H ₂ NOC-pipe
K63	iPrN(Me)-	C-H	Cl	4-HO-pipe
K64	iPrN(Me)-	C-H	Cl	4-MeO-pipe
K65	iPrN(Me)-	C-H	Cl	4-H ₂ O ₃ P-pipe
K66	iPrN(Me)-	C-H	Cl	4-(EtO) ₂ (O)P-pipe
K67	iPrN(Me)-	C-H	Cl	4-NC-pipe
K68	iPrN(Me)-	C-H	Cl	4-H ₂ NOC-pipe
K69	iPrN(Me)-	C-F	F	4-HO-pipe
K70	iPrN(Me)-	C-F	F	4-MeO-pipe
K71	iPrN(Me)-	C-F	F	4-H ₂ O ₃ P-pipe
K72	iPrN(Me)-	C-F	F	4-(EtO) ₂ (O)P-pipe
K73	iPrN(Me)-	C-F	F	4-NC-pipe
K74	iPrN(Me)-	C-F	F	4-H ₂ NOC-pipe
K75	Me ₂ N-	C-H	Cl	4-HO-pipe
K76	Me ₂ N-	C-H	Cl	4-MeO-pipe
K77	Me ₂ N-	C-H	Cl	4-H ₂ O ₃ P-pipe
K78	Me ₂ N-	C-H	Cl	4-(EtO) ₂ (O)P-pipe
K79	Me ₂ N-	C-H	Cl	4-NC-pipe
K80	Me ₂ N-	C-H	Cl	4-H ₂ NOC-pipe
K81	Me ₂ N-	C-F	F	4-HO-pipe

(Table 38 Continued)

No	R ¹	X	Y	R
K82	Me ₂ N-	C-F	F	4-MeO-pipe
K83	Me ₂ N-	C-F	F	4-H ₂ O ₃ P-pipe
K84	Me ₂ N-	C-F	F	4-(EtO) ₂ (O)P-pipe
K85	Me ₂ N-	C-F	F	4-NC-pipe
K86	Me ₂ N-	C-F	F	4-H ₂ NOC-pipe

(Table 39)

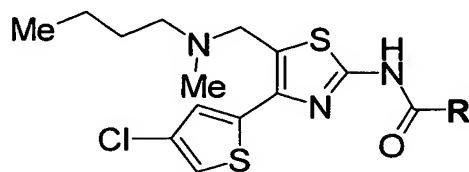


No	R	No	R
L1	3-HOCH ₂ -pyrr	L29	3-H ₂ O ₃ P (CH ₂) ₂ -pyrr
L2	3-HO(CH ₂) ₂ -pyrr	L30	3-H ₂ O ₃ P CH ₂ -azet
L3	3-HOCH ₂ -azet	L31	3-H ₂ O ₃ P (CH ₂) ₂ -azet
L4	3-HO(CH ₂) ₂ -azet	L32	(EtO) ₂ (O)P-(CH ₂) ₂ NH-
L5	3-HO-azet	L33	(EtO) ₂ (O)P-(CH ₂) ₃ N(Me)-
L6	MeO(CH ₂) ₃ NH-	L34	(EtO) ₂ (O)P-(CH ₂) ₂ N(Me)-
L7	MeO(CH ₂) ₂ NH-	L35	(EtO) ₂ (O)P-(CH ₂) ₃ O-
L8	MeO(CH ₂) ₃ N(Me)-	L36	(EtO) ₂ (O)P-(CH ₂) ₂ O-
L9	MeO(CH ₂) ₂ N(Me)-	L37	3-(EtO) ₂ (O)P-pipe
L10	3-MeO-pipe	L38	3-(EtO) ₂ (O)P-pyrr
L11	3-MeO-pyrr	L39	4-(EtO) ₂ (O)P-CH ₂ -pipe
L12	4-MeOCH ₂ -pipe	L40	4-(EtO) ₂ (O)P- (CH ₂) ₂ -pipe
L13	4-MeO(CH ₂) ₂ -pipe	L41	3-(EtO) ₂ (O)P-CH ₂ -pyrr
L14	3-MeOCH ₂ -pyrr	L42	3-(EtO) ₂ (O)P-(CH ₂) ₂ -pyrr
L15	3-MeO(CH ₂) ₂ -pyrr	L43	3-(EtO) ₂ (O)P-CH ₂ -azet
L16	3-MeOCH ₂ -azet	L44	3-(EtO) ₂ (O)P-(CH ₂) ₂ -azet
L17	3-MeO(CH ₂) ₂ -azet	L45	HOCH(Me)(CH ₂) ₂ NH-
L18	NC-(CH ₂) ₃ NH-	L46	HOCH(Me)CH ₂ NH-
L19	NC-(CH ₂) ₂ NH-	L47	HOCH ₂ CH(OH)CH ₂ NH-
L20	NC-(CH ₂) ₃ N(Me)-	L48	HOCH(Me)(CH ₂) ₂ N(Me)-
L21	NC-(CH ₂) ₂ N(Me)-	L49	HOCH(Me)CH ₂ N(Me)-
L22	NC-(CH ₂) ₃ O-	L50	HOCH ₂ CH(OH)CH ₂ N(Me)-
L23	NC-(CH ₂) ₂ O-	L51	HOCH(Me)(CH ₂) ₂ O-
L24	3-NC-pipe	L52	HOCH(Me)CH ₂ O-
L25	3-NC-pyrr	L53	HOCH ₂ CH(OH)CH ₂ O-
L26	4-NC-CH ₂ -pipe	L54	Mor
L27	4-NC-(CH ₂) ₂ -pipe	L55	MsNH(CH ₂) ₃ -NH-
L28	3- NCCH ₂ -pyrr	L56	MsNH(CH ₂) ₂ -N(Me)-

(Table 39 Continued)

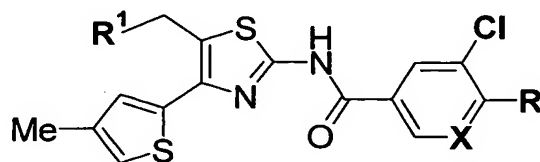
No	R	No	R
L57	3-NC(CH ₂) ₂ -pyrr	L73	MsNH(CH ₂) ₃ -N(Me)-
L58	3-NCCH ₂ -azet	L74	HO ₃ S-(CH ₂) ₃ -NH-
L59	3-NC(CH ₂) ₂ -azet	L75	HO ₃ S-(CH ₂) ₂ -N(Me)-
L60	4-Me-3-oxo-pipa	L76	HO ₃ S-(CH ₂) ₃ -N(Me)-
L61	5-oxo-1,4-diazepan-1-yl	L77	3-THP-O-
L62	Me ₂ NOC-pipe	L78	4-THP-O-
L63	3-F-pyrr	L79	2-THF-CH ₂ O-
L64	4-F-pipe	L80	3-THF-CH ₂ O-
L65	4-(tetrazol-5-yl)-pipe	L81	3-THF-NH-
L66	4-H ₂ O ₃ P-(CH ₂) ₂ -pipe	L82	4-THP-NH-
L67	3-H ₂ O ₃ P-CH ₂ -pyrr	L83	2-THF-CH ₂ NH-
L68	H ₂ NO ₂ S-(CH ₂) ₂ -NH-	L84	3-THF-CH ₂ NH-
L69	H ₂ NO ₂ S-(CH ₂) ₃ -NH-	L85	3-THF-N(Me)-
L70	H ₂ NO ₂ S-(CH ₂) ₂ -N(Me)-	L86	4-THP-N(Me)-
L71	H ₂ NO ₂ S-(CH ₂) ₃ -N(Me)-	L87	2-THF-CH ₂ N(Me)-
L72	HO ₃ S-(CH ₂) ₂ -NH-	L88	3-THF-CH ₂ N(Me)-

(Table 40)



No	R	No	R
M1	quinolin-2-yl	M5	quinolin-7-yl
M2	quinolin-3-yl	M6	2-HO-quinolin-6-yl
M3	quinolin-4-yl	M7	2-MeO-quinolin-6-yl
M4	quinolin-6-yl		

(Table 41)



No	R ¹	X	R
N1	cBuN(Me)-	C-H	4-HO-pipe
N2	cBuN(Me)-	C-H	mor
N3	cBuN(Me)-	C-H	4-H ₂ O ₃ P-pipe
N4	cBuN(Me)-	C-H	4-NC-pipe
N5	cBuN(Me)-	C-H	3-oxo-pipa

(Table 41 Continued)

No	R ¹	X	R
N6	cBuN(Me)-	N	4-HO-pipe
N7	cBuN(Me)-	N	mor
N8	cBuN(Me)-	N	4-H ₂ O ₃ P-pipe
N9	cBuN(Me)-	N	4-NC-pipe
N10	cBuN(Me)-	N	3-oxo-pipa
N11	iBuN(Me)-	C-H	4-HO-pipe
N12	iBuN(Me)-	C-H	mor
N13	iBuN(Me)-	C-H	4-H ₂ O ₃ P-pipe
N14	iBuN(Me)-	C-H	4-NC-pipe
N15	iBuN(Me)-	C-H	3-oxo-pipa
N16	iBuN(Me)-	N	4-HO-pipe
N17	iBuN(Me)-	N	mor
N18	iBuN(Me)-	N	4-H ₂ O ₃ P-pipe
N19	iBuN(Me)-	N	4-NC-pipe
N20	iBuN(Me)-	N	3-oxo-pipa
N21	2-Me-pyrr	C-H	4-HO-pipe
N22	2-Me-pyrr	C-H	mor
N23	2-Me-pyrr	C-H	4-H ₂ O ₃ P-pipe
N24	2-Me-pyrr	C-H	4-NC-pipe
N25	2-Me-pyrr	C-H	3-oxo-pipa
N26	2-Me-pyrr	N	4-HO-pipe
N27	2-Me-pyrr	N	mor
N28	2-Me-pyrr	N	4-H ₂ O ₃ P-pipe
N29	2-Me-pyrr	N	4-NC-pipe
N30	2-Me-pyrr	N	3-oxo-pipa
N31	iPrN(Me)-	C-H	4-HO-pipe
N32	iPrN(Me)-	C-H	mor
N33	iPrN(Me)-	C-H	4-H ₂ O ₃ P-pipe
N34	iPrN(Me)-	C-H	4-NC-pipe
N35	iPrN(Me)-	C-H	3-oxo-pipa
N36	iPrN(Me)-	N	4-HO-pipe
N37	iPrN(Me)-	N	mor
N38	iPrN(Me)-	N	4-H ₂ O ₃ P-pipe
N39	iPrN(Me)-	N	4-NC-pipe
N40	iPrN(Me)-	N	3-oxo-pipa